AMERICAN ASSOCIATION OF FELINE PRACTITIONERS

5th WORLD FELINE VETERINARY CONFERENCE

Complex DISEASE MANAGEMENT

Exploring Feline Comorbidities

October 31 – November 3, 2019

Hilton San Francisco Union Square ▪ San Francisco, CA

www.catvets.com/education

PROCEEDINGS

Complex Disease Management

Exploring Feline Comorbidities

THURSDAY, OCTOBER 31, 2019

Pre-conference Day

TIME	SESSION TITLE	SPEAKER	ROOM	SPONSOR/ PARTNER
7:30 - 10:00 am	Feline-Friendly Handling Workshop**	Dr. Ilona Rodan	Imperial Ballroom	
	PRE-CONFERENCE DAY*			
10:00 - 11:50 am	**Early Morning Learning Sessions**			
10:00 - 10:55 am	Keeping Calm Under Pressure: Hypertension & Comorbidities in Cats	Dr. Andrew Sparkes	Continental Ballroom 1-4	
10:55 - 11:50 am	Mind & Body: How Emotions Can Impact Feline Health	Dr. Andrew Sparkes	Continental Ballroom 1-4	
11:50 - 1:15 pm	**Food for Thought Luncheon**			
12:15 - 1:15 pm	Between a Rock & a Hard Place: Diagnosis & Management of Constipation	Drs. Jolle Kirpensteijn & Susan Little	Continental Ballroom 5-6	
1:30 - 5:30 pm	**ABVP/AAFP Seminar & Social**			
1:30 - 2:20 pm	Localizing Feline Dyspnea	Dr. Christopher Byers	Continental Ballroom 1-4	
2:20 - 3:15 pm	Update on IMHA	Dr. Christopher Byers	Continental Ballroom 1-4	
3:15 - 3:45 pm	Refreshment Break		Continental Ballroom 5-6	
3:45 - 4:35 pm	Practical Approach to Feline Hypotension	Dr. Christopher Byers	Continental Ballroom 1-4	
4:35 - 5:30 pm	Acute Pancreatitis: What Do We Really Know?	Dr. Christopher Byers	Continental Ballroom 1-4	
5:45 - 7:45 pm	Halloween Party Welcome Reception *All attendees invited*		Continental Ballroom Foyer	Boehringer Ingelheim

*Pre-conference Day Registration Required. Additional fees apply.
**Separate Registration Required from Pre-conference Day. Additional fees apply.

Session Descriptions

This conference offers concurrent Veterinary Tracks, a Technician/Nurse Track, and a Practice Management Track that will allow attendees the opportunity to customize their learning experience. All of the Tracks offer cutting-edge feline research and the latest information in feline medicine. You can choose to follow one Track exclusively or you can jump between tracks, based on your own interests and needs.

Feline-Friendly Handling Workshop

Ilona Rodan, DVM, DABVP (Feline)

Introduction

Feline-friendly handling can be incorporated successfully into any type of practice. These handling principles and techniques minimize feline stressors, increasing feline welfare, client loyalty, job satisfaction, and human safety. Understanding the cat is the foundation of feline-friendly handling as cats are unique as the only solitary hunter that can live amicably with people.[1] As such, they have strong survival instincts and protective mechanisms when they perceive threats - not uncommon during veterinary visits. It is important to recognize and alleviate feline stressors that surround veterinary care, using a combination of Cat Friendly Practice and Feline-Friendly Handling. Please review the following webinar in preparation for the workshop: *Feline-Friendly Handling (Updated 2018):* www.catvets.com/handling-webinar. The handling workshop will provide additional information and techniques to prevent stressors and to facilitate working with cats that continue to display fear or other negative emotions despite our best efforts.

How veterinary visits impact feline welfare – the good and the bad

What is welfare?

Our veterinary and technician oaths state that we will protect animal health and welfare, which refers to both physiological and psychological well-being – an individual animal's ability to cope mentally and physically at a particularly point in time.[2] Although veterinary professionals strive to care for our patients' physical health, our education about feline psychological well-being has often been inadequate. Many cats suffer from poor welfare, unable to cope, habituate or adapt to unfamiliar situations or individuals, both in the home environment and veterinary practice.

Cats are sentient beings, able to experience both positive and negative experiences, with an awareness to seek the positive and avoid the negative.[2] Feline welfare is enhanced by an environment and experiences that minimize negative states such as anxiety and boredom while promoting behaviors that cats find rewarding - including normal species-specific behaviors.[3] Each cat needs a sense of control or choice, and the ability to find pleasure and comfort in their environment.[2]

Short- and long-term impacts of veterinary care on welfare

Cats have good long-term memory, and previous negative experiences can impact how a cat will respond in the future.[4,5] Restraint, unrecognized and unaddressed fear or pain can lead to aggression at subsequent visits. A negative veterinary experience in young puppies can impact their long-term welfare, leading to chronic fear or anxiety, and this likely occurs in kittens too.[6] Some cats may do better with house calls, but many cats do well in practices as long as measures are taken to provide a safe space, respectful handling, and familiarity of team members.[7] In fact, cats do well during second visits when the veterinarian and team members are familiar.[7]

Impact of veterinary visits on cat owners

Owners love their companion cats, both divulging their innermost secrets to them and crediting them with reducing their stress level more frequently than do dog owners.[8] However, recent information indicates that only 54.3% of households with cats as the only companion animal visit the veterinarian at least once/year.[9] The average number of annual veterinary visits was 0.7%, with stress of the veterinary visit as a major factor.[9] Most cat owners think their cats show impaired welfare during all stages of the visit, starting at home, in the waiting room, moving to the exam room, on the exam table, and after returning home.[10] Stress worsens with additional experiences and negatively impacts other situations.[10] Restraint, pain, and anxiety lead to aggression directed towards veterinarians and owners.[10] Owners seek a veterinarian based on their knowledge, kindness, compassion, and respectful and gentle handling of cats, and will change veterinarians if their cat is not handled in this manner.[9,10]

Understanding the cat in the veterinary context

Understanding the feline species is important for respectful handling and feline welfare. Whereas other domestic animals evolved from pack animals, cats evolved from *Felis silvestris lybica,* a solitary hunter.[1] Cats are essentially solitary survivors, needing to protect themselves from potential dangers. As its ancestors, the domestic cat is a territorial animal, and safe territory is critical to provide security, a sense of control, familiarity, predictability, and increased coping ability.[11] In the practice, safe territory is often a familiar place to hide, such as the bottom half of the carrier or a cat bed. Feline pheromones are chemical messages used to communicate with other members of the species, allowing cats to protect territory from others without physical altercations. Posturing, facial expressions, and vocalizations can all be used to communicate with other species and other cats that do not heed their chemical

messages. Lastly – and only lastly – they will fight to protect self. Feline stressors associated with veterinary visits result in these protective communications and behaviors by triggering emotional motivations in the brain that mediate functions contributing to the survival and well-being of the individual.[12]

Understanding the individual cat and why some are challenging to work with

A cat's behavioral responses at the practice are based on their genetics, the parents' sociability to humans, and its own experiences at any age, but especially during the sensitive period of development, between 2-9 weeks of age.[13] If a kitten is handled positively and frequently during this stage and by people of different genders and ages, including children, the cat will be more amenable to handling and less fearful of even unfamiliar people for life.[14.] On the other hand, a cat that was never socialized to people early in life will be more fearful during veterinary visits. Also, a previous negative veterinary experience, such as a fearful or painful event, will often result in a highly reactive cat at future visits (see "Fear/Anxiety).

Feline stressors during veterinary visits

Multiple potential stressors surround the veterinary experience, most of which can be alleviated. Stressors often start at home, and continue from waiting area to wards. Any stressor can negatively impact the cat, but multiple stressors are cumulative, affecting the cat even more than the sum of the individual stressors.[12] Recognizing and preventing stressors in the veterinary practice must be an essential goal for feline welfare and human safety. Animal welfare experts and practicing veterinarians identify the major stressors that impact the welfare of feline patients as the attitudes of veterinary professionals, a novel environment, separation from owners and other pets, unfamiliar people and animals, olfactory and auditory stimulation, lack of optimal analgesia, and physical restraint.[6,15]

Physical restraint and what's wrong with it

There are many articles that allude to the fact that cats are more reactive with physical restraint, increasing the likelihood of human injury.[16-20] Surveys indicate that injury rates are reduced for veterinary professionals that are in Cat Friendly Practices and that use more gentle handling techniques. In 2018, scientific evidence was published to demonstrate that cats respond negatively to tight restraint when compared to passive handling techniques.[19] Tight restraint consisted of placing a cat in lateral recumbency, with its' back against the holder, while holding front and back legs, allowing little to no movement. Passive handling allowed the cat to stand, sit, or lay down, with the ability to move head, body, and limbs. Odds of struggling was 8.2 times higher with tight vs. passive restraint, exams took longer with full restraint, and cats were more likely to escape after it. Body postures and other negative behaviors that demonstrated signs of distress were noted with tight restraint.[18] Additionally, cats showed aversion towards an environment where they had been tightly restrained, choosing to spend more time in the environment where they were passively handled.[19] Another study indicated that a complete physical examination was possible without any restraint in 76% of cats.[20]

In addition to tight restraint, scruffing, shaking, forceful stretching, and restraint gloves lead to loss of sense of control, leading to poor feline welfare, negative emotions, and undesirable behavioral responses, including increased potential for aggression.[12] International Cat Care has developed "Pledge to go 'scruff-free'", https://icatcare.org/scruffing, Which advocates to not scruff cats and explains that it is further increases feline distress and potential for human injury.

Emotions triggered by practice stressors

Emotions in cats are instinctual motivations rather than feelings.[21] Positive or negative situations trigger emotional responses in the brain that mediate functions that contribute to the survival and well-being of the individual.[12] Our goal in practice is to promote the positive and prevent or reduce the negative.

Positive emotional motivations

Positive emotional systems provide pleasure. The systems are desire, social play, lust and care.[12] As lust is associated with sexual activity, care with parental care of kittens, and social play occurs especially between kittens, the only positive emotion to incorporate into general practice is desire seeking.

Desire seeking:

The desire seeking system motivates cats' interest to explore, anticipating increased opportunity to find resources needed for survival - food, water, and shelter.[21] It includes predatory or foraging behavior, object play, curiosity, and social interaction.[22] Learning and behavior modification that is associated with positive reinforcement or rewards occurs through the desire seeking system.[22] Desire seeking helps to facilitate the appointment for cats and subsequently everyone else.

Negative emotional motivations

Stressors trigger negative emotional responses that function to support survival. The negative emotions are fear, anxiety, frustration, pain, and grief, and we see all except for grief during feline handling.[12] More than one negative emotional system can be triggered at the same time; for example, fear or anxiety can exacerbate pain, further impairing an individual's ability to cope.[23, 24] Preventing or alleviating the cat's negative emotions by reducing stressors facilitates successful handling.

Fear and *anxiety* are part of the same emotional system.[12] Fear is a normal emotional motivation to what the cat considers threatening, whereas anxiety is the anticipation of a potential threat. A cat is anxious if it anticipates that something negative will happen because they felt fearful or painful at a previous visit. An anxious cat may lunge and hiss even before being touched, as it anticipates that something bad will happen, remembering a previous negative experience. Fear responses negatively impact feline welfare and the ability to learn to new tasks.[25]

Frustration is the inability to access safety or receiving less or no reward than anticipated.[26] It is seen in two different situations, with one being is a kitten or cat receiving little or no attention or reward than anticipated, such as in a caged cat pawing at people for food, play, or attention. The other is inability to access safety such as with tight restraint or removing a cat from a cage or carrier against its will.[26] The latter situation can escalate quickly to aggression.[26]

Pain is both a sensory and an emotional response, impacting not only physical function but also the emotional welfare of the patient.[27] Degenerative joint disease, lower urinary tract disease and periodontal disease are all well well-recognized painful and chronic conditions in cats. Since fear or anxiety can exacerbate pain, stressors must be minimized in addition to administrating analgesia.[28]

Behavioral responses to negative emotions

The behavioral response is communicated to us by feline posturing, facial expressions, vocalizations, and abnormal behaviors. The primary goal of feline communication is to prevent physical altercations. Although humans cannot detect the cat's chemical communication, we can learn to recognize the meaning of vocalizing, body posturing, and facial expressions. Being able to "read" the cat aids in developing a plan to work with that cat to prevent further arousal and human injury. Table 1 describes behaviors associated with negative emotions. More specific behavioral responses are addressed in "Handling cats with negative emotions".

Handling principles based on understanding the cat

Surveys of animal welfare experts, practicing veterinarians, and cat owners, as well as studies comparing tight and passive restraint confirm what many have thought to be the case for a long time. We will address each point in the presentation, and the proceedings focus on points not well recognized previously.

Mindshift and the courage to change

The attitudes of veterinary professionals cause feline distress and poor welfare.[6, 15] Our judgements about cats and their behaviors impact how we react to cats. Changes in the mindshift of individuals and the practice culture are needed to recognize that there are no bad cats, but rather distressed cats. The majority of owners and some veterinary professionals think cats act out of spite, but they do not.[29] Practices need to educate clients to carrier train cats and veterinary teams to use non-threatening feline handling techniques. The knowledge and courage to change a practice culture requires more than education alone; follow-up and accountability are also essential.

Promoting positive feline emotions

The desire seeking system motivates cats to explore to find food, water, and shelter. It includes predatory or foraging behavior, object play, curiosity, social interaction, and learning through positive reinforcement or rewards. Cats learn quickly when rewarded and can be trained to enter a carrier voluntarily and to travel within, making the carrier and transport much more pleasant for the cat and owner. Positive handling and a brief home "exam" familiarize the cat to examination in the practice. Treats provided during training at home and at the veterinary practice allow exploring or foraging for food and positive anticipation. Medical care can be provided for many cats while they are given treats or a toy to play with.[25] Gruen, et al. used behavioral conditioning to train cats to voluntarily enter a carrier, be transported and handled, working slowly, positively, and at the individual's level.[25] Resources for client education on carrier training are readily available through AAFP, CFP, and the owner website, Cat Friendly Homes. Promote positive emotions at the practice by providing food or treats, play, or positive attention to cats that are calm or curious. It is important to recognize that cats will only take treats or food if they are not already stressed.[10]

Safe territory and the option to hide

The familiar carrier, favored bedding, toys and treats brought from home promote positive and reduce negative emotions. In fact, all cats - whether motivated through positive or negative emotions - need safe territory for survival,

especially in a novel environment.[30] Hiding is an important coping strategy in an unfamiliar environment, and studies have proven that the option to hide reduces distress and negative emotions, enhancing human safety.[30-33] Hiding options should be provided during appointments, hospitalization, and boarding. Providing hiding options in hospital and boarding suites also allows for more restful sleep and improved recovery.[30-32] These patients are more likely to approach people and retreat less, [32] facilitating removal of the cat from the suite.

Although the cat feels hidden, thorough examination and completion of many procedures can occur with little or no assistance due to the cat's increased sense of security in its safe territory or hiding place. The handler's position to the side or behind the cat – and not in front – furthers the cat's sense of being hidden. Hiding options that allow easy access for veterinary care include the bottom half of a hard-sided carrier, a soft-sided carrier, a cardboard box with an opening on the side, a high-sided or igloo cat bed, and towels rolled into a donut-shape to surround a cat. The latter is an excellent choice for patients recovering from anesthesia to facilitate needed care.

Respecting feline senses and how cats perceive the practice

Cats perceive the world very differently than we do, with their olfactory and auditory systems usually far superior to ours. Visual and tactile senses will be discussed during handling, but an understanding of the cat's superior senses of smell and hearing can aid in development of a better practice environment.

Olfactory: Cat noses are about one thousand times more sensitive than ours, and cats also possess a vomeronasal organ, another means of detecting scent.[34] Unfamiliar or unpleasant scents can occur both at the veterinary practice and with house calls. Those smells include those of unfamiliar people and other companion animals. Disinfectants with scent, perfumes, and rubbing alcohol should be avoided when possible. Dilute chlorhexidine solution has no scent and works well for sample collection and catheter placement. Recommend also that clients bring bedding for the carrier or a cat bed from home with either the client's or the cat's own scent. Use of feline synthetic pheromone (Classic) within the carrier and at the practice may also be helpful.

Auditory: Cats can hear both higher and lower frequencies, as well as ultrasound, making their hearing superior to most mammals, including people and dogs. [35, 36] Loud noises such as phones, centrifuges, washers, dryers, human voices, and the sounds of other animals can all cause fear. Because of their excellent sense of hearing, this includes human voices that we consider in the normal range; use only soft voices. Keep away from vocal animals and equipment noise whenever possible. When not possible, use white noise and/or classical music which is the music genre cats do best with.[37]

Analgesia

Chronic feline pain is common, with signs varying dependent on the location and severity of the pain. Up to 92% of cats have degenerative joint disease (DJD), impacting the joints of the limbs and/or spine. [38]Although more common in older cats, DJD can occur in cats of all ages. [38] Periodontal disease is also very common in cats. Painful and potentially painful cats should be given analgesia prior to examination and potentially painful procedures (e.g., radiographs or venipuncture). [39] The facial expressions most important to recognize with acute feline pain are widening of the muzzle and between the ears. [39, 40]

Less is better

Fewer handlers: The examiner can handle most cats by themselves, preferably within the bottom half of the carrier or within another hiding area. Cats that like to sit on laps may prefer to be snuggled in the examiner's lap, facing the client or hidden within bedding. A maximum of 2 handlers is best, and sedation or rescheduling a preventive care appointment is recommended if the cat cannot be handled comfortably. When indicated, give sedation also in the exam room.

One location: Taking the cat directly to the exam room upon arrival to the practice prevents arousal and allows acclimation to the room. If a room is not available, a concierge service is highly successful, with cat and owner remaining in a temperature-controlled vehicle until the exam room is ready, avoiding a waiting room with other pets. If not possible, have a feline-only waiting area and cover the carrier with a towel impregnated with synthetic feline pheromones.

Keeping the cat in one room allows the cat to acclimate to that room.[41] For outpatients, the exam room is the least stressful room, with no visibility of unfamiliar animals, the least amount of unfamiliar people, and reduced sights, sounds and smells of the busy practice. Preparing the exam room in advance with all that may be needed for the feline patient – towels, a scale, stethoscope, otoscope, ophthalmoscope, blood pressure machine, and blood and urine collection equipment – prevents the commotion of frequent trips in and out of the exam room. In many practices, this is not possible, and all equipment should be brought in when the doctor enters the room. If transport to another area of the practice is necessary, it should be done with the cat in the closed and covered carrier, avoiding high traffic and noisy areas.

If hospitalization or boarding is needed, the cage or suite should be prepared with prior to removing the cat from the exam room. The suite should always contain a hiding place. To retain familiarity and the cat's scent, keep the cat in the same suite unless soiled, spot cleaning as needed.[42] If the cat hidden in its hiding area needs to be removed from the cage, remove the hiding area with the cat within. Often, exams and pain scores can be done while the cat is partially hidden.

Preferred areas of touch
Cat prefer human touch in the same areas that socially bonded cats groom one another, strengthening the social bond.[43,44] These areas are over the cat's facial glands, which produce pheromones to communicate between members of the same species. The facial glands consist of the temporal glands between the ears and eyes where the fur is often thinner, the cheek glands, perioral glands around the corners of the mouth, and the submandibular gland on the chin. Massaging, petting, or gently rubbing these areas while remaining to the side or behind the cat helps to reduce feline distress.

Appointment flow
Bring the cat directly from the vehicle to the exam room and allow the cat the choice to remain in the carrier while obtaining the history. This is a great time to assess the emotional state of the cat and to think about the best options for handling this specific cat. The majority of cats prefer to remain within the carrier – even if not carrier trained - throughout the visit. Most of the examination can be done with the cat within the carrier and facing away from you, further alleviating feline distress and increasing accuracy of exam findings and diagnostic tests. For cats that choose to remain within the carrier, do whatever is possible within the carrier. In these cases, the cats will be weighed at the end of the examination. If the cat displays signs of fear (see below), cover the cat loosely with a towel when the carrier lid is removed for further hiding opportunity. Only remove the cat from the carrier once, thus reducing arousal. When all that needs to be done with the cat is completed, allow the cat to return to the carrier prior to further client communication and education.

The order of the examination should start with what is least distressing for that individual cat, usually auscultation of heart and lungs. Most cats do best if orthopedic and oral examinations are performed at the end of the examination because these regions are more likely to be painful, and cats are usually less familiar with owners touching them. If the cat has chosen to remain hidden within the carrier, the retinal exam can be done after auscultation and palpation. Only then should the cat be weighed. Move the scale covered with a towel close to the carrier. Place a treat on the towel and allow the cat to choose to go onto the scale by itself. If the cat stays in the carrier, zero the scale and gently pick up the cat only a few inches above the carrier and scale, and place on the scale. Diagnostics, starting with blood pressure, and treatments should follow. Most Cat Friendly Practices do not take temperatures in apparently healthy and awake patients. There is a wide variability between axillary and rectal temperatures, making axillary temperature measurements unreliable.[45]

Allowing clients to remain with their cats during all out-patient procedures usually reduces stress for both cats and owners, and increases client appreciation and respect for the veterinary care provided in your practice. It is helpful for most cats to have the owner remain in the room minimally for the blood pressure if they do not want to observe diagnostics.[42]

Handling cats with negative emotions
Handling the fearful or anxious cat that freezes (inhibition). Consider why the cat is fearful based on its genetics and previous experiences. Although the cat that "freezes" might seem easy to work with, it is important to recognize that these cats are fearful, and our behavior can impact its fear response and our safety. If we allow the cat to remain in a hiding place such as the bottom half of the carrier or high-sided cat bed, the cat will likely remain quiet and hidden throughout the exam, and is more amenable to handling. If instead the cat is forcibly put in a place or position that it does not choose and/or is handled in ways that it finds threatening, the fear response is likely to progress to fleeing or aggression.12 If carrier training has not occurred, it should be recommended. An anxiolytic may also be indicated for future visits.

Handling the fearful cat that 'flees' (avoidance)
Chasing a cat that flees will exacerbate fear and greatly increase the potential for self-protective aggression. Once a cat is aroused, it can take time to calm down. Provide a quiet, dark or soft-lit room with several readily accessible hiding options and leave the cat alone. Owner education, having the owner "drop off" the cat, and team members leaving the cat alone for preferably an hour – and moving on to the next appointments to keep on time – are helpful.

If the owner does not wish to leave the cat or if the cat is highly aroused, rescheduling the appointment for an apparently healthy cat is a good option. The client should be educated carrier training and bringing familiar objects to the visit, and an anxiolytic should be precribed. Remind owners to keep the cat within the carrier with the door closed

for future appointments and to let veterinary professionals remove the cat from the carrier.

Handling the fearfully aggressive cat
It is important to remember why the cat is aggressive. This is not a 'bad' or 'evil' cat, but rather a frightened cat that is attempting to protect itself. Sedation or anesthesia with analgesia should be administered to prevent potential injury and exacerbated feline fear and anxiety at future visits. Anxiolytics should be recommended for future appointments.

Handling cats with frustration
The following steps will dramatically reduce frustration and the associated aggression: allowing a cat that is pawing at a carrier to exit; respectful handling; providing a place to hide within a cage or moving them to a private area. For cats that are highly aroused with frustration, sedation or anesthesia is recommended. As frustration also occurs when a cat is not given attention or food when anticipated, consistent times for feeding, play, and human attention if desired helps prevent this negative emotion.

Handling the painful cat
As cats demonstrate subtle signs of pain and chronic pain is common in cats, handle each cat as potentially painful. All handling techniques discussed today are recommended to prevent pain. Analgesia should be given to painful and potentially painful cats either at home or during appointments for cats with chronic painful conditions such as DJD, periodontal disease, and dermatological conditions, including pruritis. Procedures such as imaging and anal sac expression also require analgesia. The reader is referred to the AAFP Feline Anesthesia Guidelines for more specific information on sedation and anesthesia, and the AAFP/AAHA Pain Management Guidelines 2007 to help recognize painful conditions and the 2015 guidelines for more specifics on feline degenerative joint disease and analgesia.

Pharmacological treatments
Pharmacotherapy can significantly lessen a cat's distress but it should never be used to replace a cat-friendly environment and gentle handling procedures. Rather, it should be used concurrently when indicated.

Anxiolytic prior to veterinary visit – who needs it and what to give
Gabapentin has been proven to be an excellent anxiolytic in cats, and more effective than other drugs (more references available during workshop).[46,47] In practice, the general dose is 100mg given 90 minutes to 3 hours prior to the visit.

Cats that have had a negative experience previously at the veterinary practice benefit from a combination of carrier training and gabapentin at future visit(s). Additionally, cats born to feral parents, those not socialized to people during the sensitive period, or that have had a bad experience at any time in life - even if not associated with veterinary visits – are good candidates to receive gabapentin prior to veterinary visits. It should be given at home and can be given before outpatient appointments and admittance for procedures including anesthesia or boarding. Anxiolytics are not effective if a cat is already aroused.

When sedation is recommended and what to use
There is less need for sedation when cats are given gabapentin prior to veterinary visits. However, there are times when gabapentin is not administered prior to an appointment, or additional therapy is needed. Most important is to recognize when to reach for sedation, and it is early on. Examples are if it takes more than 2 people to respectfully and safely handle a patient, if the cat is hissing and lunging and turning towards you while still in a closed carrier, if struggling, or if painful procedures where analgesia is insufficient. Anesthesia is also a good option for some of these patients, and often the preference for an apparently healthy cat is to reschedule the appointment, combining an examination with a needed procedure (e.g., dental prophylaxis). In these cases, send home a prescription of gabapentin and advice on carrier training.

Benefits of sedation for examination of certain patients and for procedures include less physical restraint, decreased stress, simpler airway management, avoidance of inhalants and rapid recovery.[48] Good feline sedation options are dexmedetomidine and alfaxalone, usually in combination with other drugs such as opioids for analgesia. Alfaxalone (2mg/kg) is apparently safer in cardiac disease, and occult heart disease is not uncommon in cats. This information has not been confirmed in cats with hypertrophic cardiomyopathy, but is based on studies in healthy cats indicating no change in echocardiographic measurements with alfaxalone, [49] whereas dexmedetomidine may cause decreased heart rate, increased blood pressure, and echocardiographic changes of both atrial and ventricular size and function.[48, 50]

Butorphanol provided superior sedation and a lower incidence of vomiting than buprenorphine when given intramuscularly in combination with dexmedetomidine.[51]

Conclusion

Feline-friendly handling techniques prevent feline stressors, subsequently reducing the negative emotions and behaviors that team members often consider difficult.

Table 1. Recognizing the behavioral response to negative emotions helps recognize when different methods for handling and working with cats are important.

Body Postures	Facial Expressions	Inhibition of normal behaviors
Hiding Crouched Head lower than rest of body In the back of the carrier or cage Tense muscles Hypervigilant Piloerection Trembling Sweaty paws Unsheathing claws Swatting Lunging	Dilated or oblong pupils Pupils fixated on the subject Ears held back or rotated to the side Whiskers splayed out Lip licking Rapid blinking Drooling Mouth open – hissing, shrieking	Inappetence or not eating Failure to groom Failure to eliminate Lack of play behavior Failure to sleep - Hypervigilant - Feigned sleep

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Keeping Calm Under Pressure: Hypertension & Comorbidities in Cats

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Introduction

Systemic hypertension is a well-recognised condition in cats. As in humans, there is evidence that blood pressure tends to increase as cats age but hypertension is also more commonly diagnosed in older cats (typically >6-7 years of age). Hypertension can be classified as either 'primary' where there is no identifiable underlying disease (perhaps up to 20% of feline cases), or 'secondary' where it is associated with a concomitant disease (accounting for 80%+ of feline cases) [1, 2]

Once hypertension is identified, careful management and ongoing assessment of blood pressure is important to ensure adequate control and to prevent 'target organ damage'. Target organs damaged by hypertension may include the eyes, kidneys, heart, brain.

Hypertension and target organ damage (TOD)

Hypertension is most likely to cause damage to tissues with a rich arteriolar supply, including the eyes, brain, kidneys and cardiovascular system. Hypertensive damage to these tissues is known as 'target organ damage' (TOD). The aim should be to diagnose and manage hypertension so that the manifestations of TOD are minimized or absent, although in some cases severe (and sometimes permanent) TOD may have already occurred.

Hypertensive ocular damage is commonly reported in cats, possibly reflecting the relatively late diagnosis often made. Hyphemia, retinal haemorrhage, retinal oedema, alterations to the diameter and increased tortuosity of retinal arterioles, and partial or complete retinal detachment can all be seen. In the brain, hypertension can lead to both cerebral oedema and arteriosclerosis but neurologic signs are non-specific and include disorientation, seizures, ataxia, reduced mentation and vestibular signs. A presumptive diagnosis of hypertensive encephalopathy is usually made if neurological signs improve following normalization of BP with treatment.

Left ventricular hypertrophy is a well-recognized complication of hypertension and can be accompanied by gallop sounds on cardiac auscultation and more rarely congestive heart failure. Hypertension is well documented as a causal factor of human chronic kidney disease (CKD) and can lead to progression of CKD in both humans and dogs. In cats, hypertension may cause glomerulosclerosis and renal arteriosclerosis which suggests the kidneys are a target organ for hypertensive damage as well.

Underlying causes of hypertension

As it is estimated that around 80% of hypertensive cats have secondary hypertension, it is important that a thorough search is done to identify potential underlying diseases when hypertension is identified (and conversely, BP should be monitored carefully in all cats with diseases known to predispose to hypertension).

The most common and important diseases associated with secondary hypertension in cats are:

- Chronic kidney disease – this is the single most important cause of secondary hypertension in cats and it has been reported that hypertension is present in around 20%-60% of cats with CKD[2].
- Hyperthyroidism – hypertension has been reported in as many as 10-20% of hyperthyroid cats[1,3], but may also be seen in a significant proportion of cats once their hyperthyroidism has been successfully managed.[1,3] In a recent study of 282 cats diagnosed with hypertension, CKD was identified in 46% and hyperthyroidism in 25%[9]
- Primary aldosteronism – as in humans, some evidence exists that in these cases the hypertension may respond better to a combination of spironolactone (a diuretic and aldosterone antagonist) and amlodipine[3]
- Hyperadrenocorticism (HAC) – although this is an unusual endocrinopathy in cats and the prevalence of hypertension with this disease is uncertain, there is at least one report of severe systemic hypertension in an affected cat[4] which resolved following bilateral adrenalectomy, and experience in other species suggests hypertension may occur quite commonly.
- Pheochromocytomas – these are rare in cats but the autonomous production of catecholamines can lead to severe hypertension.[5] It has been suggested that initial management of hypertension in cats with a pheochromocytoma should involve the use of alpha-blockers (eg, phenoxybenzamine), with the possible subsequent introduction of beta-blockers if severe tachycardia persists.[5]
- Diabetes mellitus – although there is a strong link between diabetes and hypertension in humans, there is little current evidence to suggest hypertension is prevalent in cats with diabetes mellitus, and severe hypertension in diabetic cats appears to be uncommon. However, the mean BP in cats with diabetes has been found to be higher than in healthy age-matched controls, suggesting there is a potential link.[6]

- Other diseases are also likely to predispose towards hypertension including acromegaly, hypothyroidism, and hyperparathyroidism.

Measurement of blood pressure in cats

Systemic blood pressure (BP) is measured in conscious cats using indirect methodologies – generally via either Doppler sphygmomanometry or oscillometric methods. Doppler has been regarded as more accurate with traditional oscillometry being less reliable in measuring BP and with a poorer correlation to directly measured BP. However, high definition oscillometric (HDO) equipment has been introduced, which appears to overcome many of the problems associated with traditional oscillometry. Both Doppler and HDO equipment can therefore be recommended for clinical use.

Importantly, whether Doppler or HDO equipment is used to assess BP, studies have shown that it is *only* the measurement of systolic arterial pressure (SAP) that is accurate with either technique.[1] Measurements of diastolic and/or mean arterial pressures are inaccurate, and these values should be ignored. However, SAP is considered perfectly adequate as isolated diastolic hypertension appears to be rare.

Recommended protocols

SAP is labile and varies both within and between individuals, being affected by arousal, stress, activity, age, genetic makeup and other factors. Furthermore, assessment of SAP can be affected by external variables including the operator, environment, equipment, position of the cat, and site of measurement. Using standardised protocols (see https://icatcare.org/sites/default/files/PDF/CEVA-BP-Booklets/ISFM%20BP%20recommendations%20English.pdf as well as the link to the videos https://www.youtube.com/playlist?list=PLp5A851vjwHCuYMD-uZK8CqKBRlDjskzk) to increase reproducibility is important, but SAP measurement can be readily and quickly performed in most cats[1]:

1. Environment: SAP should be measured in a calm quiet environment, away from other animals, with minimal personnel. The choice of room depends on clinical needs and circumstances but generally BP should be assessed with the cat away from other animals and away from noise, lighting or smells that may contribute to anxiety and stress. Using familiar bedding and/or synthetic facial pheromone (Feliway Classic) is likely to be helpful.
2. Acclimatisation: A minimum of 5–10 minutes should be allowed for the cat to acclimatise to the room before BP is measured. Allowing the cat to wander freely in the room and interact with people if it so chooses will help.
3. Personnel: The people present in the room should remain the same during the acclimatisation period and during BP measurement, and BP measurement should be performed by a trained individual (a feline-empathetic veterinary nurse or technician is often ideal). When measuring BP for an outpatient, having the owner present to reassure the cat in a quiet, gentle way can help. In general, having the minimum number of people needed in the room is preferable.
4. Restraint and positioning of the cat: Only minimal and gentle restraint should be used to keep the cat in a comfortable position. If the cat becomes agitated, stop and take a break to allow the cat to settle down rather than using stronger restraint. The cat should be allowed to choose a comfortable position – for example lateral or sternal recumbency, sitting, or standing, and try to keep the cat in the same position throughout the procedure.
5. Choice and position of cuff: The correct cuff width is 30–40% of the circumference of the site where it is being applied. Incorrect size can lead to a false high BP if the cuff is too small, or false low BP if too large. The choice of site for the cuff is often determined by operator preference and by the tolerance of the cat. There is some evidence that the forelimb may be easier and more reliable for Doppler and that the tail may be preferable for HDO. Limbs should be manipulated gently and with care as some cats may resent this and for others (eg, with osteoarthritis) this may be painful. Cuffs should fit snuggly where applied but should not restrict blood flow.
6. Measuring BP: Before measuring BP it may be advisable to inflate and deflate the cuff a few times to allow the cat to get used to the procedure. When measuring SAP it is recommended that the first measurement is discarded and then the subsequent 5–7 measurements are recorded and mean of these used to calculate the SAP. There should be <20% variability between these readings, and no consistent downward (or upward) trend in readings. If these criteria are not met, further readings are recommended to improve accuracy. If there is doubt over the validity of the measured SAP, the procedure should be repeated, perhaps after another period of quiet acclimatisation, or at a later time point.
7. Written records: Accurate records should be kept of all important aspects of the BP measurement so that the procedure can be repeated in the same manner in the future (for comparable results). Details should include the environment/room used, people present and operator, position of the cat, size of the cuff, site of cuff placement, equipment used, individual SAP measurements, and calculated mean SAP.

Use of Doppler or HDO equipment

To get reliable results, it is important that both Doppler and HDO equipment are used following recommended protocols. [1] For HDO equipment this includes using the tail where possible (to minimise interference from muscle

movement) and to always use the equipment linked to a computer monitor using the supplied software so that a visual inspection of the data can be assessed to ensure movement artefacts have not given a false reading.

How is hypertension defined?
Systemic BP varies substantially both within and between individuals, and there is a tendency for BP to rise with age.[7,8] Where hypertension occurs, development of clinical disease (eg, target organ damage – TOD) may also depend on the individual and the rate of change in BP as well as the absolute BP. Further, the methods used to determine BP in clinical practice are not precise and several other factors (see earlier) can contribute to variability in measured BP making it difficult to define 'normal' BP in cats and what cut offs to use for any intervention. Because the circumstances under which BP is measured will vary from one clinic to another, where possible, each clinic should try to define their own reference values for BP, with BP measurements being included as part of routine health checks. However, published data suggests that few cats exhibit any evidence of TOD with a SAP lower than 160 mmHg and the following risk categories for SAP have been suggested as general guidelines[1,2]:

- SAP <140 mmHg: Minimal risk of TOD
- SAP 140-159 mmHg: Low risk of TOD
- SAP 160-179 mmHg: Moderate risk of TOD
- SAP ≥180 mmHg: High risk of TOD

However, it should also be noted that stress-associated increases in BP (or 'white coat' hypertension) can temporarily increase SAP significantly in excess of 180 mmHg in some cats and so care is needed in interpretation of individual values and where doubt exists over the validity of the measurement it should be repeated after a period of rest (or after a few days).

When should hypertension be treated?
The ISFM Guidelines on Management of Hypertension in Cats[1] suggests the following criteria for assessing when to institute anti-hypertensive therapy in cats:

1. If indirect SBP is ≥150 mmHg on a single occasion **and** there is clear evidence of ocular or neurological TOD. However, if clinical signs do not respond appropriately to anti-hypertensive therapy, the diagnosis should be reassessed
2. If indirect SBP is ≥160 mmHg on at least two separate occasions and there is evidence of any TOD including ocular, neurological, cardiac or kidney damage
3. If indirect SBP is ≥170 mmHg on at least two separate occasions and the clinician does not consider 'white coat hypertension' to be a likely cause
4. If indirect SBP is <150 mmHg but where there is clear evidence of active ocular TOD. In this situation cats should be monitored carefully and that if there is any doubt about the diagnosis of hypertension the need for long-term therapy should be re-assessed.

Management of hypertension
Although management of an underlying disease may sometimes lead to resolution of secondary hypertension, the underlying disease cannot always be reversed (eg, CKD) and irrespective of concomitant diseases, the hypertension itself will still need to be managed. The initial therapeutic goal should be to reduce the SAP to <160 mmHg[1] and in the longer term perhaps to aim for a SAP <140-150 mmHg.[1]

Amlodipine besylate has long been regarded as the drug of choice for management of hypertension in cats, and is now licensed for feline use in some countries (including Europe, Australia and New Zealand). It is a potent peripheral arterial dilator with minimal effects on the heart and is successful as a mono-therapy in as many as 60-100% of cats.[1] Oral administration is recommended at a starting dose of 0.625mg/cat (or 0.125mg/kg) q24h. The dose should be doubled if response is inadequate after the first 1-3 weeks. Further, in cats with a higher initial SAP (≥200 mmHg) a higher starting dose (1.25 mg/cat or 0.25 mg/kg q24h) may be preferable. Rarely, doses up to 2.5 mg/cat or 0.5 mg/kg q24h may be needed to control hypertension.

Telmisartan is an angiotensin receptor blocker that has recently gained approval as an agent for the management of feline hypertension in some countries. It is licensed for use at a dose of 1.5 mg/kg, orally, BID for 14 days then 2.0 mg/kg q24h, with further dose adjustments made according to clinical need. The efficacy of telmisartan (based on early published data) appears similar to amlodipine, at least in the treatment of cats with SAP between 160 and 200 mmHg, but the drug may take considerably longer to achieve maximal effect which may make it less suitable than amlodipine for management of severe hypertension or when there is concern regarding ongoing TOD.
Other drugs (eg, angiotensin converting enzyme inhibitors and beta-blockers) appear to have poor efficacy in the management of feline hypertension, but may be considered as additional agents if response to other treatments is

inadequate. In some cases, the underlying disease may affect the choice of adjuvant therapy such as beta-blockers for cats with severe tachycardia, alpha-blockers for cats with pheochromocytomas, spironolactone in cats with hyperaldosteronism and ACE inhibitors or ARBs for cats with proteinuria and CKD.

Cats on anti-hypertensive therapy should be monitored carefully and regularly to ensure adequate BP control without risk of causing hypotension. It is recommended that cats without evidence of TOD be reassessed at least every 7-10 days, initially, aiming to achieve a SAP <160 mmHg within 1-2 weeks and then <140-150 mmHg over the following several weeks.[1] It has been suggested that SAP should not be allowed to go below 110 mmHg.
Cats with a high initial SAP (≥200 mmHg) or with TOD should have their BP and clinical signs monitored closely during the first 24-72 hours.[1] If necessary the initial dose of amlodipine can be repeated at 4–8 hour intervals up to a maximum of 2.5 mg/cat in the first 24 hours.[1]

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Mind & Body: How Emotions Can Impact Feline Health

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Introduction

The causes of stress in cats – a solitary, hunting, highly territorial and semi-domesticated species - are well documented, but in the veterinary context whether a cat comes into a novel environment, such as the veterinary clinic, or whether the veterinarian visits the cat in its home environment, either situation can lead to cats becoming acutely stressed, and the cat may also suffer stress for many other reasons too.

Neural, hormonal and immunological systems all participate in the stress response but two classic hormonal pathways are activated during a stress response - the sympatho-adrenal and the glucocorticoid responses (the latter mediated by activation of the hypothalamic-pituitary adrenal [HPA] axis). An acute stress response is generally an adaptive and protective mechanism, but may still result in changes that have important consequences in the clinical patient. Chronic activation of stress responses may often have significant pathophysiological and clinical consequences and, for example, chronic increases in catecholamine concentrations can have significant adverse cardiovascular effects and prolonged glucocorticoid release has a well-recognised role in immunosuppression.

Stress responses to environmental events are complex and vary between individuals. While both genetic and environmental factors influence an individual's response, recent research on the long-term effects of early life stressors (ELS) and how these may affect stress responses and disease later in life in many mammalian species has revealed that [1–10]:

- Environmental stressors experienced during pregnancy can expose the unborn foetus to maternal stress hormones, that can result in epigenetic and neurohormonal changes which markedly affect their responses to adverse events later in life
- ELS during early life may have similar profound long-term implications
- The changes that occur are often unpredictable, and may depend in part on the nature, timing and duration of any ELS, and also on positive nurturing experiences and the balance between the two. In general, exposure to strong pre-natal or ELS can result in sensitization of stress response systems to subsequent events.
- Exposure to ELS can also negatively affect adrenal development (sometimes *suppressing* subsequent cortisol production) as well as 'rewiring' the central stress response system (particularly through epigenetic modulation of gene expression), resulting in long-term neuroendocrine changes. In studies of rats, epigenetic changes in response to early-life exposure to stress were found to affect the expression of more than 900 genes.

Such observations help explain the profound effect ELS can have on gene expression, physiology and behaviour and explains why ELS can increase the susceptibility to the development of certain psychological and physical diseases, including infections and idiopathic chronic pain syndromes in humans.[4, 10, 11] Conversely, effective environmental enrichment can prevent or mitigate their effects[4].

Stress responses are also the result of an individual cat's experiences and may be learned over time. A cat's perception of a given stressor is influenced by a number of factors, including their genetics, personality, level of socialization, and prior experience, as well as the duration, frequency, severity and predictability of the stressor. In addition, the cat's ability to perceive that the stressor is escapable, or not, will profoundly influence the cat's response. The emotional (behavioural) responses of cats are learned both through associative learning (classical conditioning) and through the consequences or their behavioural actions (operant conditioning). In some instances, cats may become sensitized to particular stressors, creating strong negative emotional associations that ultimately result in acute or even chronic fear, anxiety or frustration, all of which may in turn affect the animal's behaviour, wellbeing, immunity and health. In some instances, cats may fail to adapt or habituate to environmental stressors or may become sensitized to particular stressors, creating strong negative associations that may generalize and affect their behaviour in a variety of contexts. Thus, the influence of a cat's learning process over time is likely to have a substantial impact on its health and wellbeing, either by increasing or decreasing its risk for physical and behavioural health problems, depending on the individual cat.

The effect of acute stress on physiological parameters

There is a very poor correlations between subjective stress scores in cats and objective changes in physiological parameters attributable to stress.[12] Therefore, the veterinary care team must always consider the impact of the stress response on any parameters assessed, and try to minimise the stress involved.

Stress hyperglycaemia (SH) causes a transient rise in blood glucose and is one of the classic examples of a stress-induced physiological response in cats. Studies suggest up to 1/3 of cats coming to a clinic may exhibit SH, some with very high glucose concentrations. This can complicate the diagnosis and management of diabetes but a feline-friendly environment and handling techniques in the clinic may help to dramatically reduce the prevalence of SH.
Many other physiological parameters can be affected by stress, some more predictably than others. These include:

- Increase in rectal temperature, blood pressure, heart rate and/or respiratory rate
- Paradoxical alkaluria (due to elevated respiratory rates)
- A 'physiological leucogram' (neutrophilia and sometimes lymphocytosis and a raised PCV) typically attributed to catecholamine release
- A 'stress leucogram' (neutrophilia, lymphopenia and sometimes monocytosis) typically seen with longer duration stress and mainly attributed to higher glucocorticoid concentrations
- Increased endogenous cortisol concentrations and urinary cortisol:creatinine ratios
- Exaggerated (or sometimes inadequate[13]) serum cortisol responses to exogenous ACTH administration
- Possibly decreased secretory immunoglobulin A

These alterations in physiological parameters have an important impact on our interpretation of clinical findings and often make diagnosis of abnormalities or disease states more challenging. In some situations, assessment of parameters (such as heart rate, respiratory rate, urine pH and blood glucose) in the home environment may improve evaluation and monitoring of cats, but this is not inevitably beneficial. Attempts should always be made to ensure the environment is as feline-friendly as possible including the approach to handling of cats. In the clinic environment, examining the cat on its own bedding and/or the use of synthetic pheromones (eg, Feliway Classic) in the clinic and in the cat carrier can be helpful.

Stress and lower urinary tract disease

Most cats with chronic recurrent lower urinary tract signs (LUTS) have what is commonly referred to as feline idiopathic cystitis (FIC). In these cats, a recognised cause of LUTS cannot be found and the signs may spontaneously resolve within several days.

The underlying cause of FIC remains uncertain, and not all cats may be suffering from the same condition. Nevertheless studies have revealed some marked similarities between at least some cats with FIC and IC/BPS (Interstitial Cystitis/Bladder Pain Syndrome) in humans.[5] Investigations of affected cats have revealed[14, 15]:

- Urine samples are consistently sterile
- On cystoscopy, sub-mucosal petechial haemorrhages (non-pathognomonic) may be observed
- Changes in urinary glycosaminoglycan concentrations
- Damage to the epithelial barrier in the bladder
- Evidence of sensory neuronal abnormalities
- An exaggerated acoustic startle response
- Evidence of increased sympatho-neuronal activation
- Evidence of smaller adrenal glands and reduced glucocorticoid production
- Aggravation or induction of clinical signs following exposure to environmental stressors

More recently it has also been recognised that many cats that suffer with FIC may also show co-morbid disorders including behavioural abnormalities, gastrointestinal signs, dermatological signs and cardiovascular abnormalities. Many of these observations are similar to humans with IC/BPS[16], and it is now thought that stress plays an important role in this syndrome. It is possible that affected cats may have an underlying genetic susceptibility and that there may also be epigenetic effects through neonatal or early life exposure to a stressful environment (see earlier). This may increase susceptibility to chronic LUTS; if these cats are subsequently placed in a provocative environment (exposed to significant adverse events), clinical disease may ensue.

These findings may help to explain why a history of stressful events can often be identified in affected cats, and why a variety of co-morbid signs are often seen, the pattern of which may result from inherent genetic traits.[17] They also help to explain why multimodal environmental enrichment has become a successful method of managing FIC.
Despite these findings, many aspects of FIC in cats (and IC/BPS in humans) remain unresolved. Additionally, while effective environmental enrichment may largely control clinical signs, the role of other interventions (including dietary modifications; increasing water intake; drugs aimed at modifying the bladder epithelial barrier function, and reducing inflammation and/or pain) remain uncertain, with at least some studies suggesting potential beneficial roles.

Until future research helps address these issues, multimodal environmental enrichment currently includes:

- Reducing inter-cat aggression and conflict in households
- Reducing exposure to identified stressors
- Avoiding punishment

- Offering choice when introducing change (food, water, litter, etc.)
- Improving litter box management including the use of unscented clumping litter
- Provision of climbing structures, with viewing and resting perches
- Use of scratching posts
- Increasing animate and inanimate play and interactions
- Providing audio and visual sensory stimulation and consider pheromone therapy (eg, Feliway Classic, Feliway Friends [EU] / Feliway MultiCat [US] and Feliscratch)

In addition to helping resolve LUTS in affected cats, such environmental enrichment has been shown to reduce signs of fear and anxiety in affected cats and to reduce other signs of co-morbid disorders.

Stress and infectious diseases

The link between chronic stress and immunosuppression is well established, and is known to increase susceptibility to infection and immune-mediated diseases. Both catecholamines and glucocorticoids may be involved in mediating immunosuppression through various mechanisms.[18] The specific role of stress has been studied in some diseases better than others, and some of the best knowledge in cats relates to the role of stress in respiratory disease (especially infection with feline herpesvirus – FHV). Interestingly in humans there is also a well-established link between psychosocial stress and acute respiratory tract infection.[19] From studies of FHV infection in cats it is known that[20]:

- Virtually all cats infected with FHV become long-term or life-long latent carriers of the virus
- Latently infected cats can experience 'reactivation' of infection which is most likely to occur after periods of stress and immunosuppression and the greater the stress the greater the amount of virus shed
- There is a lag phase of around 4-11 days from the onset of a stressor to the start of re-shedding of FHV, and the duration of re-shedding is variable
- Reactivation and viral shedding can be associated with recurrent clinical signs and can be a source of infection to other cats

There is also evidence that the use of synthetic facial pheromones diffusers (Feliway Classic) may help to alleviate some signs of FHV infection in previously infected cats when they are stressed[21].

Other situations where there is direct evidence that stress may play a role in influencing and modifying the response to infectious agents include increasing the risk of development of feline infectious peritonitis[22] in cats exposed to coronavirus infection, persistent viraemia in cats exposed to feline leukaemia virus, and gastrointestinal infections (especially in a shelter environment).

Stress and gastrointestinal disease

In humans, acute stress is recognised to have varying effects on the gastrointestinal (GI) system – for example causing loss of appetite, diarrhoea, or vomiting. Chronic stress may also be important and irritable bowel syndrome (IBS) is a common example of a stress-mediated GI disease. Interestingly, co-morbidity with IBS and syndromes such as IC/BPS is commonly seen in humans.

It is well-recognised that acute stress can contribute to decreased eating and drinking in cats (as evidenced by the frequent observation of a reduced appetite in cats entering a new environment or being confined to a hospital cage or shelter) and that acute stress can contribute to constipation as an adverse event (e.g., placing a cat in a new environment) may directly lead to a reduction in frequency of defecation. However, less is known about the effect of chronic stress in feline GI disease.

It has been estimated that up to 10% of dogs with large bowl diarrhoea may have a form of IBS[23], often linked to environmental stressors.[23, 24] Although this syndrome has not been well researched, there is evidence that improving the environment improves the disease. There is less published data on IBS in cats, although it is strongly suspected to occur. Vomiting, constipation, diarrhoea (either large or small bowel), and defecating outside the litter tray are all recognised as 'sickness behaviours' that may go along with signs of FIC in some cats, and are therefore suspected to be manifestations of stress in some cats.

Anecdotally, an IBS-type disease certainly seems to occur in cats, in which typically episodes of vomiting or diarrhoea appear to be precipitated or exacerbated by environmental stressors, and where investigations reveal no other specific underlying causes. Such cases, as in dogs with IBS, may respond to dietary change and to environmental enrichment. In this context, witnessing a response to a dietary change should not necessarily be interpreted as a dietary intolerance or dietary allergy – in many cases re-introduction of the original food may not necessarily provoke recurrent clinical signs so changing the diet may alter the human-pet relationship in subtle ways that have beneficial effects.

Stress and obesity
Stress-induced or emotional over-eating is recognised in humans and is a risk factor for obesity. It has also been suggested that chronic stress (and associated over-eating) might have a role to play in obesity in some cats.[25] In barren or multi-cat environments with social stress and competition for resources it is conceivable that stress might induce hyporexia in some cats, whereas in others it might actually motivate them to eat more.

Hyperthyroidism
Cats with hyperthyroidism tend to have markedly increased urinary cortisol:creatinine ratios[26] suggesting that, as in humans, the disease is associated with hypercortisolaemia (which may contribute to some manifestations of the disease). Although not studied in cats, hyperthyroidism in humans may increase the sensitivity of various tissues (including the heart) to circulating catecholamines, contributing to the manifestations of the disease. This suggests cats with increased sympatho-adrenal stimulation as a result of stress, may potentially suffer further exacerbation of clinical signs.

Type 2 Diabetes mellitus (T2D)
In humans, there is good evidence that chronic stress leads to an increased risk of T2D[27], possibly through chronic hyperglycaemia and insulin resistance. Although studies on the role of stress in the development of T2D in cats are limited, the analogy to T2D in humans suggests that this link would be worth exploring. Irrespective of a causal link between the two, there is no doubt that stress and stress-induced hyperglycaemia is an important confounding factor in the diagnosis and management of feline diabetes.

Psychogenic alopecia
Psychogenic skin disease ('psychogenic alopecia') is perhaps the classic manifestation of a stress-induced skin disease in cats, and is characterised by overgrooming. Despite over grooming, the underlying skin may show no inflammation and owners may not even be aware the cat is overgrooming. Although there is compelling circumstantial evidence that this disease is a genuine entity, with some cases demonstrating a direct link between stress and the onset or resolution of overgrooming, this is a diagnosis that is impossible to 'prove' as there is no diagnostic test to confirm its presence. Further, purely psychogenic skin disease appears to be rare in cats[28–30]

Although psychogenic skin disease is rarely diagnosed as a stand-alone entity in cats, it is possible that concurrent psychological factors (stressors) may play a role along with allergy (or potentially other causes of pruritus) in some cases. A variety of stressors might be involved, but the constant pruritus itself may add to or trigger a stress response, and potentially the stress may exacerbate pruritus and overgrooming. In human medicine, the field of pyschoneuroimmunology has described various links between neuroendocrine functions, stress and allergic skin diseases but much less information is available for cats. Examples of associations between allergy and stress in humans include, for example[31–33]:

- Studies show an increased frequency of admission to hospital for allergy and asthma-related problems at times of conflict (a major stress event),
- Some studies have demonstrated greater skin reactivity to exogenous allergens in association with stress
- Sputum eosinophil counts in asthma patients were also found to be higher at the time of stress
- In rats experimentally sensitised to an oral allergen, some were exposed to a ringing bell at the same time as being exposed to the allergen. Over time, the rats exhibited anaphylaxis just to the sound of the bell without exposure to the allergen, demonstrating that classical conditioning can play a vital role in allergic disease

Although further work is needed in cats, there is no reason to anticipate they would be different from other species, and thus stress is likely to have a contribute to at least some cases of allergic skin disease and probably other allergies in cats as well. Addressing stress in cases of pruritic and inflammatory skin disease and in cases of other allergies is thus an important consideration and may positively impact disease control and cat welfare. It might, for example, lead to a reduction in the required dose of steroids or other anti-inflammatory drugs.

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Between a Rock & a Hard Place: Diagnosis & Management of Constipation

Jolle Kirpensteijn, DVM, PhD, DACVS, DECVS & Susan Little, DVM, DABVP (Feline)

Constipation is the infrequent and difficult evacuation of feces with retention of feces within the colon and rectum. Obstipation is intractable constipation. The typical feline patient is middle-aged and male.[1] Many cats have one or two episodes of constipation without any further problems. However, chronic constipation and obstipation may result in megacolon where a dilated large bowel is poorly responsive to therapy. Cats with idiopathic megacolon have generalized dysfunction of colonic smooth muscle.[2] Some of the more common underlying causes of constipation include certain drugs, stressors and litter box aversion, difficulty in defecating (pain, neurologic problems), excessive fecal bulk, dehydration (e.g., associated with chronic renal disease), intra- or extra-luminal colon masses, narrowed pelvic canal, and idiopathic megacolon. Whenever possible, the underlying cause should be identified and corrected.

Clinical signs and diagnosis

The clinical signs of constipation are typically obvious to the owner, such as tenesmus, and scant hard dry feces, sometimes with blood. However, cats will also strain in the litter box due to lower urinary tract obstruction and owners may misinterpret this as due to constipation. Occasionally, constipated cats will have intermittent diarrhea as the colon is irritated due to hard dry fecal matter. Other clinical signs are non-specific, such as vomiting, inappetence and lethargy.

Physical examination confirms the presence of large amounts of feces in the colon sometimes accompanied by abdominal pain. The colon often palpates as a long firm tube or feces may be palpated as discrete concretions. A careful evaluation (e.g., musculoskeletal system, caudal spinal cord function, anorectal area) should be made for underlying causes. A rectal exam should be performed, under sedation if necessary, for masses, pelvic fracture malunion and anal gland abnormalities. A minimum database (CBC, serum chemistries/electrolytes, urinalysis) should be assessed, especially to determine hydration and electrolyte status and identify underlying diseases such as chronic renal disease. Survey abdominal radiographs are useful to confirm the diagnosis and assess severity as well as to evaluate for potential underlying causes, such as previous pelvic trauma and arthritis. The diameter of the colon on a lateral view should be approximately the same length as the body of the 2nd lumbar vertebra.[3] Enlargement of the colon beyond 1.5 times the length of the body of the 5th or 7th lumbar vertebra has been proposed as indicating chronic dysfunction and megacolon.[3,4] One study of 11 cats with megacolon found the mean diameter of the colon was 2.7 times greater than the length of the 7th lumbar vertebra (median: 2.4, range 1.8-3.3).[5] In some cases, further diagnostics such as a barium enema or colonoscopy may be warranted.

Acute Management

The first step in management is correction of dehydration with intravenous fluid therapy followed by removal of obstructing feces. One or two doses of a 5 mL microenema containing sodium lauryl sulfoacetate (MicroLax) is easily administered and will usually produce results within 20-30 minutes in mildly affected cats. Obstipated cats will require warm water or isotonic saline enemas (5-10 mL/kg). Safe additions to the water include mineral oil (5-10 mL/cat), or docusate (5-10 mL/cat), but do not administer the two together. Soaps or detergents may be irritating to an already compromised colonic mucosa. Lactulose solution can also be administered as an enema (5-10 mL/cat). Sodium phosphate containing enemas must not be used as they can induce life-threatening hypernatremia, hyperphosphatemia and hypocalcemia in cats.[6] Enemas are administered slowly with a lubricated 10-12 French feeding tube. In severe cases, manual manipulation of the feces via abdominal palpation or per rectum (manual disimpaction) under general anesthesia with endotracheal intubation (in case of vomiting) is also required. In these cases, opioids should be administered for pain relief.

An alternative to enemas is administration of an oral polyethylene glycol (PEG 3350) solution (e.g., CoLyte, GoLytely). A nasoesophageal tube is placed and the solution is given as a slow trickle (6-10 mL/kg/hour) over 4-18 hours. Defecation usually results in 6-12 hours. In a retrospective study of 9 cats, median time to defecation was 8 hours and the median total dose of PEG 3350 was 80 mL/kg.[7] No adverse effects were noted.

Long term management

In addition to management of any underlying conditions, long term medical treatment involves a combination of prokinetic agents, laxatives and dietary therapy. Cisapride stimulates contraction of feline colonic smooth muscle.[8] A typical starting dose is 2.5 mg/cat BID, PO and it is better absorbed when given with food. Doses up to 7.5 mg/cat, TID have been reported. The drug is only available from compounding pharmacies in most countries. It has been withdrawn from the human market due to the occurrence of life-threatening arrhythmias in predisposed individuals (not known to occur in cats). It may be prudent to advise clients handling cisapride to wear gloves. Hyperosmotic

laxatives include lactulose and PEG 3350; they stimulate colonic fluid secretion and propulsive motility. The dose of lactulose solution is 0.5 mL/kg, PO, BID-TID. Lactulose is also available as crystal meant to be mixed in liquids for human use (Kristalose). A suggested dose is 3/4 tsp. BID with food. PEG 3350 is available as a powder meant to be mixed in liquids for human use (MiraLAX). A suggested dose for cats is 1/8 to 1/4 tsp. BID in food.

Dietary therapy has included the use of high fiber diets (>20% on as fed basis) and low residue diets. Increased dietary fiber increases the production of short chain fatty acids which stimulate feline colonic smooth muscle contraction.[9] Dietary fiber is also a bulk laxative and will increase fecal bulk, which will not be beneficial for all patients. Feeding a canned diet is often recommended to reduce fecal bulk and to ensure adequate water intake and hydration. Psyllium powder can be mixed with canned food at 1-4 tsp. SID-BID. A certain amount of trial and error is necessary to determine the best diet type for an individual patient.

In one study carried out by a manufacturer, a moderate fiber, psyllium-enriched diet showed promise in an uncontrolled study of 66 cats with recurrent constipation.[10] The diet was well tolerated and palatable. Most cats improved within 2 months and were either maintained on diet alone or with decreased doses of cisapride and lactulose than previously used.

It is also important to ensure adequate water intake by various methods, such as feeding canned diets. Most water bowls designed for cats are too small; cats dislike having their whiskers touch the side of containers. Dog water bowls are larger and more appropriate. Other methods for increasing water intake include:

- Mix water with dry diets 1:1
- Flavor water with frozen cubes of meat or fish broth
- Try distilled or filtered water, especially if the tap water supply is heavy in minerals or chlorine
- Ensure water is fresh every day, and provide multiple water bowls
- Ensure the water bowls are kept clean
- Keep food and water bowls away from the litter box
- Feed multiple smaller meals instead of one or two larger meals
- Provide a moving source of water such as a pet water fountain

Litter box modification may be helpful for cats with arthritis. Most cat litter boxes are too small and have high sides. A winter boot tray or an under-the-bed type of storage box with low sides is a better alternative to make access easier. The litter box should also be in an accessible but private area, avoiding the need to navigate stairs if possible.

Subtotal colectomy

Surgery can be considered for cats that are refractory to medical and dietary therapy.

The colon is divided into ascending, transverse, and descending portions and starts at the ileocolic sphincter. The ascending colon runs cranially, ending at the right colic flexure and continues as the transverse colon, which runs from right to left to the left colic flexure. The descending colon starts here and ends near the level of the pelvis, where the rectum begins. The cecum is a diverticulum of the proximal colon in the cat and is connected by the cecocolic orifice that lies just aboral to the ileocolic junction. The ascending and transverse colon receive its vascular supply from the ileocolic artery, a branch of the cranial mesenteric artery. The descending colon is supplied primarily by the left colic artery, the cranial branch of the caudal mesenteric artery.

There are various techniques available, including partial colectomy, subtotal colectomy, or the total colectomy. Partial colectomy is only used in cases with a distinct abnormality of part of the colon (like a diverticulum) but should not be performed in cases with generalized megacolon. A subtotal colectomy describes the removal of the majority of the colon, excluding the ileocolic sphincter and cecum. A total colectomy is performed by taking the distal ileum, ileocolic valve, cecum and most of the colon. There is still a debate on which technique is most successful as both have advantages and disadvantages. Preservation of the ileocolic valve decreases the change of diarrhea caused by bacterial overgrowth and decreased water absorption. Leaving the ileocolic valve may increase the amount of diseased colon left in the animal although good scientific data showing that there is a higher recurrence rate in subtotal colectomies is lacking. The clear advantage of the total colectomy is that the anastomosis has less tension due to the maneuverability of the ileum, the clear disadvantage is the higher chance for lasting diarrhea/loose stool and the more complicated technique. Although a number of techniques have been described to do the anastomosis, I prefer an end-to-end colo- or ileocolostomy with small (4-0/5-0) absorbable suture material.

Complications are uncommon and include contamination of the surgical site, dehiscence of the anastomosis, which both are prevented by a proper surgical technique and lower GI signs including diarrhea, soft stools and tenesmus. Diarrhea and/or soft stools normally disappear 4-6 weeks after surgery. In a minority of cats, the soft stools persist.

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Localizing Feline Dyspnea

Christopher Byers, DVM, DACVECC, DACVIM (SAIM), CVJ

Classic clinical signs of respiratory distress include tachypnea, head and neck extension, opened mouth breathing, anxiety, cyanosis, nares flaring, abducted elbows, orthopnea, and paradoxical movement of the chest and/or abdomen. Cats readily mask disease severity, and the only evidence of respiratory dysfunction may be tachypnea and prominent respiratory motions in sternal recumbency.

The first step in examining a patient with a respiratory emergency is to perform a primary survey. If the airway is not patent, it must be cleared of obstruction and orotracheal intubation performed. An emergency tracheostomy may be needed. A clinician should evaluate the patient's breathing pattern and work of breathing; attention should be given to the phase of breathing affected. Increased inspiratory effort is associated with extra-thoracic disorders while increased expiratory effort is often due to intra-thoracic diseases. An obstructive breathing pattern indicates inappropriate movement of air in/out of the lungs and is associated with a slower respiratory rate and deeper breaths than normal. A restrictive breathing pattern is characterized by inadequate expansion of the chest wall and/or lungs, resulting in shallow tachypnea. The initial evaluation of a patient should ideally begin before touching a patient, as the breathing pattern may change with manipulation.

Upper Airway

The upper respiratory tract is simply a conduit from the nares to the glottis. Diseases of the upper respiratory tract that includes the nares, nasal cavity, pharynx, and larynx are common in cats. Upon presentation, an owner may report a patient snores and/or has exercise intolerance, dysphagia, regurgitation, and/or post-tussive retching. They may also report these clinical signs are associated with and/or exacerbated by excitement, humidity, and/or elevated ambient temperatures. Physical examination may identify referred upper airway sounds, orthopnea, bilateral elbow abduction, restlessness, dysynchronous breathing, and cyanosis. Affected patients have abnormal respiratory sounds and pattern of breathing. The classic upper airway breathing pattern is characterized by increased inspiratory time and effort compared to expiration. Stertor and/or stridor may be present depending on the site of airflow turbulence. Pulmonary crackles that form due to non-cardiogenic pulmonary edema may be auscultated. Patients affected by upper airway disorders should always be handled with minimal restraint, as they may decompensate with minimal manipulation.

Lower Airway

The lower airway is comprised of the intra-thoracic trachea, primary and lobar bronchi, and bronchiolar arborization. Feline patients are most commonly diagnosed with asthma. Foreign body obstruction must be considered, and while neoplasia can affect the lower airway, they rarely induce acute dyspnea due to their chronic, insidious nature. Pet owners may report a chronic and/or progressive history of coughing that is frequently productive although the sputum is most often swallowed. Affected patients have a respiratory pattern characterized by prolonged expiration despite normal inspiratory time and effort. Additionally, a clinician may observe abdominal effort during expiration and/or auscultate expiratory wheezes. Patients may display orthopnea, and feline patients may breathe with an opened mouth.

Pleural Space

The pleural cavity is the potential space between the parietal and visceral pleura. When this potential space is occupied by air, fluid, masses, and/or viscera, the lungs are unable to expand normally. Thus, intrapleural pressure increases and exceeds intrapulmonary pressure, effectively reducing tidal volume. An affected patient must breathe rapidly to maintain adequate minute ventilation. Classically patients manifest a restrictive breathing pattern characterized by shallow tachypnea. With reduced tidal volume, alveoli progressively collapse to cause hypoventilation and hypoxemia due to ventilation-perfusion mismatch. Thoracic auscultation varies depending on the nature of the pleural disease.

Pulmonary Parenchyma

The pulmonary parenchyma may be affected by several diseases, and a thorough history will help a clinician develop appropriate diagnostic and therapeutic interventions. While coughing is common in dogs, cats rarely have a history of chronic coughing. A history of recent vomiting should raise concern for aspiration pneumonitis/pneumonia, and patients with trauma may develop pulmonary contusions and/or non-cardiogenic pulmonary edema. Recent generalized seizure activity, electrocution, traumatic brain injury, and/or strangulation should raise concern for non-cardiogenic pulmonary edema. Patients with primary cardiac disease may develop cardiogenic pulmonary edema. Affected patients do not have a specific respiratory pattern, but frequently manifest respirations that are rapid and

deep. They may be presented with cyanosis and dyspnea, and increased abdominal effort is common. Auscultation reveals end-inspiratory crackles; alveolar fluid may be blood, purulent exudate, or transudate. Alveolar hemorrhage may occur secondary to trauma and/or coagulopathy. A patient with cardiogenic pulmonary edema may have a systolic murmur and hypothermia while a patient with pneumonia or aspiration pneumonitis/pneumonia may have pyrexia. Patients should be efficiently examined for evidence of ecchymoses, obvious soft tissue, and/or orthopedic injury and thermal injury.

Chest Wall

Common thoracic wall injuries include blunt trauma, penetrating trauma and flail chest. Blunt trauma may cause crush and shear injuries to both soft tissues and skeletal structures; the skeletal structures of the chest wall are resistant to blunt force trauma. However, muscle is uniquely sensitive to crushing injury, and when damaged in low velocity accidents may become edematous, inelastic, and may lose the ability to contract. Thoracic wall compliance decreases and work of breathing subsequently increases. This may manifest as tachypnea, but breaths may be shallow or deep; subsequent hypoxemia and/or hypoventilation are common. High velocity accidents are associated with shearing injury. While soft tissue damage to the thoracic wall rarely contributes to patient morbidity, energy may be transmitted to intra-thoracic organs to induce crush and shearing injuries at these sites. A blunt force applied laterally to the thoracic wall may cause rib fractures; pressure applied dorsoventrally to the thoracic cage infrequently results in rib and sternabrae fractures, but such injuries may contribute to reduced thoracic compliance.

Penetrating injuries to the thoracic wall are common in domestic cats. These wounds induce stretching and crushing of tissues in the direct path of penetration. While the actual chest wall penetration is frequently a minor issue, one must be aware of the potential underlying pleural and intra-thoracic injuries. The type and severity of injury directly influences how a patient is presented, and the medical team must be prepared to triage a patient in respiratory distress that needs immediate orotracheal intubation and intra-thoracic stabilization.

Flail chest results from the segmental fracture and/or dislocation of two or more adjacent ribs. This type of injury is uncommon in cats because of the inherent compliance and anatomic shape of the thoracic cage. Blunt trauma and bite injuries are the most common causes of flail chest, and concurrent pulmonary damage is a major contributor to morbidity. These contusions may lead to decreased pulmonary compliance, hypoventilation, and shunting. The pathognomonic respiratory pattern is paradoxical movement of the unstable ribs (flail segment) during respiration. Splinting due to pain associated with respiration leads to a decreased cough reflex, hypoventilation, hypoxemia and atelectasis. Several techniques for stabilization of flail chest have been reported, but the primary focus should be on oxygen supplementation, underlying intrathoracic injuries, and multimodal analgesia.

Diaphragm

A myriad of disease may induce partial or complete diaphragmatic paralysis, including pleuroperitoneal hernias, botulism and phrenic nerve damage or degeneration. The classic respiratory pattern is tachypnea with marked inspiratory excursion of the cranial half of the thorax. Paradoxical abdominal movement is also common and may be due either to thoracic displacement of abdominal viscera during vigorous inspiration or an inability to maintain abdominal girth during inspiration.

Non-Respiratory Causes

There are multiple causes of tachypnea and dyspnea that do not directly arise from the respiratory tract. A common example is non-pyogenic hyperthermia. Measurement of body temperature is essential in patients presented with respiratory signs, and appropriate cooling measures should be implemented when hyperthermia is documented. Intracranial diseases may stimulate the medullary respiratory center. Patients with intracranial diseases may have abnormal respiratory patterns, and neurological examination often identifies other deficits that aid in determining a definitive diagnosis. Pain and acid-base disorders also induce tachypnea without hypoxia in patients. Abdominal distension is common cause of tachypnea and dyspnea.

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Update on IMHA

Christopher Byers, DVM, DACVECC, DACVIM (SAIM), CVJ

General Immunologic Principles

Anti-erythrocyte antibodies bind to specific epitopes of erythrocyte autoantigens on red blood cell (RBC) surfaces. These autoantigens are thought to be glycophorins and other membrane antigens (e.g.: Band 3, calpain). Immune-mediated hemolytic anemia is believed to also have an inheritable component. Friedenberg *et al* documented a strong association between two polymorphic positions in exon 2 of one allele in DLA-79 and multiple immune-mediated disease (including IMHA). Erythrocytes are most commonly opsonized by immunoglobulin (Ig) G (IgG1 > IgG3). Erythrocytes are less frequently opsonized by IgM and IgA. Opsonized erythrocytes are phagocytosed by mononuclear cells. During extravascular hemolysis, the Fc component of anti-erythrocyte antibodies bind to Fc receptors on mononuclear cells in the spleen, resulting in their destruction. Complement may be activated when enough antigen-antibody complexes are present on the surface of opsonized erythrocytes. Immunoglobulin M is a more effective activator of the complement cascade. Via the classical complement pathway, the C1 complex is activated, leading to the synthesis of C3b fragments and ultimately the cylindrical membrane attack complex (C5b | C6 | C7 | C8 | C9) that induces intravascular hemolysis. Hepatic Kupfer cells may also phagocytose erythrocytes opsonized by C3b, thus providing another mechanism for extravascular hemolysis.

Extravascular Hemolysis	Intravascular Hemolysis
Hyperbilirubinemia	Hyperhemoglobinemia
Bilirubinuria	Hemoglobinuria
Spherocytes	Ghost cells
	Shistocytes

We do not yet know why the immune system decides to target erythrocytes for destruction. This process is likely multifactorial, a combination of genetic predisposition and environmental factors like infectious agents, vaccines, drugs, and neoplasia. Thus, it's a common clinical practice to classify IMHA as either primary (idiopathic or autoimmune) or secondary. *Primary* immune-mediated hemolytic anemia (IMHA) is the most frequent form diagnosed in dogs, while the *secondary* form appears most common in cats. Definitively proving non-infectious and infectious triggers is challenging, and it must be stated correlation does not equal causation. Commonly implicated secondary causes IMHA include:

- *Infections*: feline leukemia virus (FeLV), mycoplasmosis, ehrlichiosis, babesiosis, dirofilariasis
- *Neoplasia*: lymphoproliferative disease (i.e.: lymphoma), hemangiosarcoma, poorly differentiated sarcoma
- Post-vaccinal?
- *Drugs*: TMP/SMZ, penicillins, cephalosporins, levamisole, propylthiouracil, methimazole, phenylbutazone, dipyrone, quinidine, chlorpromazine
- *Immunologic conditions*: systemic lupus erythematosus | SLE, transfusion reactions, neonatal isoerythrolysis, bee sting envenomation

Clinical Signs & Diagnosis

Immune-mediated hemolytic anemia typically affects young adult and middle-aged animals. Swann *et al* showed no sex or breed predisposition in cats with primary IMHA, but cats between 2.1-5.9 years of age were predisposed.

Clinical signs typically reflect the presence of both anemia (lethargy, weakness, pale mucous membranes, and a hemic heart murmur) and compensatory responses caused by tissue hypoxia and stimulation of the sympathetic nervous system (tachypnea, tachycardia, and hyperkinetic/bounding pulses). Some patients also show clinical signs of an ongoing immunological or inflammatory process (pyrexia, hyporexia/anorexia, lymphadenomegaly).

Patients with acute-onset IMHA are frequently severely affected, and are often very depressed, weak or even collapsed. Hyperbilirubinemia, bilirubinuria and icterus are often seen during acute and severe episodes of IMHA. Patients with extravascular hemolysis due to subacute or chronic IMHA often compensate for their lack of erythrocytes, and may be remarkably bright/alert/responsive in the face of severe anemia. In these patients, the liver often copes with the extra bilirubin released by erythrocyte breakdown so icterus does not occur. Intravascular hemolysis is relatively uncommon, and accordingly hemoglobinemia and hemoglobinuria are observed very infrequently. Ghost cells, also called ghost corpuscles and semilunar bodies, are "empty" red cell membranes that may be visualized with intravascular hemolysis.

Clinical diagnosis of IMHA requires confirmation of anemia, hemolysis and immune-mediation. Confirming anemia is straightforward, but confirmation of hemolysis and immune-mediation is more challenging. Evidence of immune-mediation includes agglutination, spherocytosis, a positive Coomb's test, and identification of anti-erythrocyte antibodies. Spherocytosis, icterus, hyperbilirubinemia, and/or hemoglobinuria (in the absence of renal tubular disease) provide evidence of hemolysis. Spherocytosis alone is not diagnostic for IMHA, and differential diagnoses include severe hypophosphatemia, coral snake envenomation, zinc intoxication, Heinz body hemolytic anemia, vasculitis, microangiopathic injury, and heritable congenital erythrocyte enzymopathies.

Common diagnostic tests performed in patients with suspected and confirmed IMHA may include:

- Minimum database: CBC | CHEM | UA
- Urine culture
- Fecal analysis (flotation, Baermann analysis)
- Diagnostic imaging: thoracic radiography | CXR; abdominal radiography | AXR; abdominal ultrasonography | AUS; echocardiography)
- Vector-borne disease screening
- Arthrocentesis
- Direct Coomb's testing
- Anti-erythrocyte antibody screening
- Coagulation testing (prothrombin time [PT] | activated partial thromboblastin time [PTT]), thromboelastrography | TEG), platelet aggregometry
- Bone marrow sampling
- Lymph node aspiration | biopsy
- Anti-nuclear antibody (ANA) measurement
- Cerebrospinal fluid analysis

A thorough diagnostic investigation is essential to identify any potential secondary causes of disease. Understandably this can be an expensive and time-consuming process, but therapeutic failure is likely if an underlying disease is not identified and treated appropriately.

Immunomodulatory Therapy

Corticosteroids: The cornerstone of IMHA therapy is corticosteroid therapy given at immunomodulatory doses. The authors of the 2019 ACVIM Consensus Statement on the treatment of IMHA did not make dosage recommendations for cats. The author believes prednisolone at a dose of 2-4 mg/kg/day in cats is a reasonable starting dose range.

Cyclosporine: Cyclosporine is a potent immunosuppressant that inhibits early T cell activation and prevents production of IL-2 and IFN-γ by T cells. These actions lead to a decrease in cell-mediated immunity and T cell-dependent B cell antibody production. An initial dose of 5-10 mg/kg PO q12 hour of the microemulsified/modified formulation is recommended. Monitoring of pharmacokinetic (peak +/- trough drug levels) and pharmacodynamic (IL-2 & IFN-γ) data is available to help guide therapeutic efficacy. Side effects include gingival hyperplasia and gastrointestinal side effects, the latter of which can be reduced by placing capsules in a freezer for storage between dosing.

Azathioprine: Azathioprine is a cytotoxic purine analog that inhibits cell division of proliferating lymphocytes. As this drug works by slowing production of immune cells, its effect is delayed. Use of azathioprine in cats is not routinely recommended due to their markedly reduced thiopurine methyltransferase activity that dramatically increases risk for toxicity. Clinical response may take 1-6 weeks. Azathioprine's main side effects include bone marrow suppression, gastrointestinal upset, poor hair growth, hepatotoxicity, and idiosyncratic pancreatitis.

Mycophenolate mofetil: Mycophenolate mofetil blocks guanine nucleotide synthesis, thus resulting in a reduction of B and T cell proliferation. Bacek *et al* reported the use of mycophenolate mofetil in two cats with primary IMHA at dose of 10 mg/kg PO q12 hr. Both cats had improved blood counts follow therapy and no adverse effects were noted.

Leflunomide: Leflunomide is an inhibitor of pyrimidine biosynthesis that is another possible immunomodulatory agent. This drug has proven efficacy in canine immune-mediated polyarthritis and feline rheumatoid arthritis. The pharmacokinetics and pharmacodynamics of leflunomide in domestic cats has been investigated but reports of clinical use are not yet available.

Intravenous Immunoglobulin: Intravenous immunoglobulin (IVIg) works by binding to the Fc receptors of macrophages, inhibiting the ability to bind to antibody-antigen complexes on RBCs. The use of this drug for use in the treatment of IMHA in cats has not been prospectively investigated.

Use of More than One Immunomodulatory Drug

In the author's opinion, patients with IMHA benefit from a multimodal immunomodulatory approach to their therapy. Most immunomodulatory agents take several days to a couple of weeks to become fully effective, so if such adjuvant medications are started only after corticosteroids have failed, a dangerous delay may ensue. Prolonged therapy anecdotally appears to be the best way of minimizing relapses, and as long-term corticosteroids often cause unacceptable side effects, 'steroid-sparing' combination therapy will usually be needed to enable reductions in steroid doses.

If one chooses not to initiate multimodal immunomodulatory therapy at the onset of therapy, additional immunosuppressive therapy should be initiated in the following situations:

- Patient presentation is consistent with severe or immediately life-threatening disease
- PCV does not remain stable (i.e.: >5% decrease in 24 hours or within first 7 days with glucocorticoid therapy)
- Patient remains blood product transfusion dependent after 7 days
- Patient is expected to develop adverse effects related to glucocorticoid use at any time during treatment

Miscellaneous Therapies

Blood Product Transfusion: Patients with clinical anemia secondary to IMHA (hemolysis) require increased oxygen carrying capacity. Clinical evidence of anemia includes resting tachycardia, tachypnea, mucous membrane pallor, hyperkinetic peripheral pulses, lethargy, and hyporexia/anorexia. Packed red blood cells should be provided to target specific endpoints of resuscitation (i.e. normalization of heart rate, resolution of tachypnea, normal lactate). Patients with concurrent hypoproteinemia may benefit from either whole blood (stored or fresh) or albumin infusions. Patients with severe thrombocytopenia can be treated with lyophilized platelets, platelet-rich plasma and/or fresh whole blood.

Splenectomy: The spleen contributed to a reduction in circulating erythrocytes and anti-erythrocyte antibody production. Although not useful for patients with intravascular hemolysis, utility for patients with extravascular hemolysis is logical. Feldman *et al* showed splenectomy may be useful for treating IMHA and Evan's syndrome that were deemed refractory to medication.

Hyperbaric Oxygen Therapy: Hyperbaric oxygen therapy increased the amount of dissolved oxygen in plasma based on Henry's Law, Fick's Law, and Boyle's Law. The benefits are numerous, including increased cellular energy production, reduced tissue and vasogenic edema, angiogenic and anti-inflammatory effects, and antimicrobial and immunomodulatory properties. This novel intervention may be associated with oxygen toxicity, barotrauma, and tympanic and pulmonary trauma. Hyperbaric oxygen therapy is contraindicated with pre-existing pulmonary bullae, pneumothorax, static electricity, and exposed metal implants.

Therapeutic Plasma Exchange: This treatment modality – also called plasmapharesis – is a highly effective method of removing unbound anti-erythrocyte and anti-platelet antibodies but has no effect on antibodies already bound to their respective target cells. Availability of this treatment modality is very limited in veterinary medicine but is growing in availability. Cowgill presented unpublished data at the 2019 ACVIM Forum (Phoenix, AZ) related to the use of TPE as a first line treatment for patients with IMHA and results were encouraging.

Thromboprophylaxis

Hemolysis induces tissue factor on monocytes and endothelial cells with subsequent activation of coagulation. Additionally, damaged erythrocytes, activated platelets and microparticles contribute to coagulation. Arterial and venous thromboembolic disease is a major factor affecting survival in cats with IMHA. Heparin (unfractionated; low molecular weight) and anti-platelet medications (clopidogrel) are commonly used for thromboprophylaxis in cats with IMHA.

To date there is a lack of controlled studies effectively documenting validated therapeutic endpoints and survival benefit. The 2019 ACVECC Consensus Statement regarding thromboprophylaxis identified IMHA patients as a population at risk for the development of thrombosis with venous thrombosis more prevalent than arterial thrombosis. The consensus statement authors recommended antithrombotic therapy for pets with IMHA. The authors noted the following important points:

- Antiplatelet drugs are more effective for arterial thromboemboli (ATE) in cats
- Anticoagulant drugs are more effective for venous thromboemboli (VTE) in cats
- Combination of clopidogrel with LMWH should be considered in cats at risk for ATE

Weaning

Many patients living with IMHA require lifelong immunomodulatory therapy. Some, however, may be weaned completely. The authors of the 2019 ACVIM Consensus Statement recommended weaning immunomodulators once the PCV has remained stable and >30% for two weeks after initiating therapy. The *initial* dosage reduction of

corticosteroid should be 25% when this drug is used as a single agent. However, when multimodal therapy has been initiated, a greater *initial* dosage reduction in the corticosteroid (i.e.: 25-50%) may be possible. As long as the PCV remains stable and >30%, a subsequent corticosteroid dosage reduction may be attempted every three weeks. If multimodal immunomodulatory therapy has been used, the *subsequent* corticosteroid dosage reduction (i.e.: 25-33%) or shorter interval (i.e.: 2 weeks) may be possible. This weaning process takes ~4-8 months without complications.

The author has not yet adopted these weaning recommendations, as he is concerned they advocate for too rapid a reduction in immunomodulatory doses. The author does not recommend initiating weaning immunomodulatory medications until a patient's PCV has been normal for at least one month. Once that milestone has been reached, the author begins weaning one immunomodulator at a time. The author prefers to wean a corticosteroid first due to owner's concerns about side effects, making a 15-25% dosage reduction once per month. Specifically, a dosage reduction is made, and then the HCT/PCV is reevaluated one week after the dosage reduction to ensure to adverse events. If the HCT/PCV is still acceptable, the patient is continued on the current corticosteroid dose for an additional three weeks. Then, the family makes another predetermined corticosteroid dosage reduction, and the patient's HCT/PCV is rechecked one week later.

This cycle of reduction and recheck is continued until the corticosteroid is completely reached. Once this happens, then one may begin weaning other immunomodulatory medications one at a time, again making a change once monthly. This weaning process takes ~5-12 months without complications.

Prognosis
Several studies have evaluated prognostic factors for mortality in cats with IMHA. The mortality rate associated has been reported to be 29-70%. Potential risk factors for death include elevated serum urea (>56 mg/dL), icterus/hyperbilirubinemia, spherocytosis, male sex, warm season, packed cell volume <20%, thrombocytopenia (<200 K/uL), total protein <6 g/dL, elevated creatinine (>0.23 mg/dL), hyperlactatemia, prolonged aPTT, elevated ALP, monocytosis, elevated IL-18 and elevated monocyte chemoattractant protein-1/MCP-1. Swann *et al* showed higher total bilirubin levels and age were significant negative prognostic factors; conversely, higher lymphocyte numbers and serum globulin concentrations were positive prognostic factors. Although several prognostic factors have been identified, results of these studies must be interpreted cautiously. Data from these studies showed many population sizes were generally small when potential confounding factors were taken into consideration.

In 2015, Goggs *et al* prospectively evaluated two previously reported illness severity scores – the Canine Hemolytic Anemia Score (CHAOS) and Tokyo score. In univariate analysis, CHAOS score ≥3 was associated with death in hospital and death within 30 days. Tokyo score was not associated with either outcome measure. ASA ≥3 was associated with death. In multivariate analysis, SIRS score, ASA classification, ALT, TBIL, urea, and creatinine were accurate in predicting outcome at discharge 82% of the time. After univariate analysis, ASA classification, TBIL, and creatinine were predictive of death by day 30 after admission.

Unpublished data from Cowgill documented a 90% survival to 30 days (compared with 54% for conventional immunomodulatory therapy), and most patients saw their PCV stabilize after 3-4 TPE treatments.

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Available upon request

NOTES:

Practical Approach to Feline Hypotension

Christopher Byers, DVM, DACVECC, DACVIM (SAIM), CVJ

Introduction

Hypotension is commonly recognized in the clinical setting, and in cats has been typically defined as a systolic blood pressure <80-90 mmHg. Intermittent or prolonged hypotension causes hypoperfusion and decreased oxygen delivery that may ultimately lead to organ damage or failure. Previously Silverstein *et al* reported hypotensive cats with lower rectal temperatures and lower packed cell volumes (PCV) had significantly lower survival rates (64% vs. 32%). So certainly, identifying the underlying cause(s) is vital to reducing morbidity and mortality.

A simplistic way to view hypotension is to consider it the manifestation as one of three causes: hypovolemia, decreased systemic vascular resistance (SVR), and cardiac dysfunction resulting in decreased cardiac output and/or reduced contractility. Obviously, there is a long list of issues that may contribute to one or more of the above three, most notably:

- Hypothermia
- Bradycardia
- Anemia
- Ionized hypocalcemia
- Acidosis

Correct Hypothermia & Electrolyte Abnormalities

Therapeutic efforts are aimed at rapidly rewarming patients during fluid resuscitation, as well as reducing additional heat loss. Resuscitative efforts should not contribute to hypothermia. It has been recommended to warm the animal approximately 1-2 degrees Celsius per hour. However, faster rates may be necessary. Moderate intravascular volume support is recommended during active rewarming in hypovolemic shock. This will support mean arterial pressure (MAP) and resolve most cases of hypothermia-induced hypotension, bradycardia, hypoventilation, and coagulopathy while avoiding volume overload.

Rewarming hypothermic animals may be accomplished by several different methods, including passive surface (e.g., blankets), active surface (e.g., Bair hugger), and active core (e.g., peritoneal and pleural lavage) re-warming strategies. Surface re-warming should always accompany active core re-warming to reduce core-to-periphery temperature gradients. During external heating, care must always be taken to prevent thermal injury by controlling the temperature of the external heating devices or placing a barrier between the heat source and the patient. Electrolytes (particularly ionized calcium), acid-base status, and electrocardiography should be monitored and derangements addressed, particularly in hypothermic patients.

FOCUS ON CARDIAC OUTPUT

Provide adequate preload

The first step of assessing cardiac output should always be to ensure adequate volume status, and thus preload. As such, one needs to provide adequate intravascular volume and stop any ongoing fluid loss. Common controversies for resuscitative fluid therapy include type of fluid (colloid versus crystalloid, and in case of colloid, synthetic versus natural), rate of administration, and end-points of resuscitation. Currently there is not "the one" recipe of fluid therapy for feline hypotension (or for any type of hypotension for that matter). Initial fluid choice depends on a variety of factors, including:

- Underlying disease process
- Colloid osmotic pressure (COP)
- Electrolyte derangements
- Acid-based status, coagulation
- Major organ function

The most commonly used fluid initially is an intravenous bolus (5-10 mL/kg) of an isotonic crystalloid – exercise caution with normal saline given its acidifying nature. Boluses of hypertonic saline (2-4 mL/kg over 20-30 minutes) and/or synthetic colloid (hydroxyethylstarches @ 2-5 mL/kg IV over 20-30 minutes) may also be needed depending on the factors listed above. If there is a confirmed or suspect secondary coagulopathy, fresh frozen plasma (FFP), and/or Vitamin K1 are indicated.

Given the guidelines of early goal-directed therapy (EGDT), the author strives to maintain PCV >25%, and thus transfuses with packed red blood cells (pRBCs) or whole blood (WB) depending on the patient's protein status when PCV is <25% with associated clinical signs of anemia. Resuscitation should be performed until several endpoints of resuscitation (EORs) are achieved, including normalization of capillary refill time (CRT), restoration of normal heart rate and pulse pressure, establishment of normothermia, urinary output >1 mL/kg/hr, and normal lactate and base excess. Once the desired endpoints of resuscitation have been reached, initiate a crystalloid and/or colloid IV CRI based on dehydration, daily requirements (45-60 mL/kg/day), ongoing losses, and COP.

Ensure Proper Contractility

Pro-inflammatory cytokines readily contribute to myocardial depression. Echocardiography frequently demonstrates poor chamber contraction contributing to reduce cardiac output. Pascoe *et al* previously evaluated dopamine, dobutamine, phenylephrine and epinephrine for inotropic effects in the isoflurane-anesthetized cats. A positive inotropic effect and improvement in cardiac output were detected with all drugs. Among the four inotropes, dopamine had the most beneficial effects. Phenylephrine increased systemic vascular resistance index with minimal effect on heart rate, but dobutamine decreased it and dopamine and epinephrine had no effect. Epinephrine was as effective as dopamine, but increased lactic acid production and base deficit significantly.

FOCUS ON SYSTEMIC VASCULAR RESISTANCE

Maintain Appropriate Afterload

Afterload is determined largely by peripheral vascular tone (systemic vascular resistance). Clinical signs of vasodilation include hyperemic mucous membranes, brisk CRTs (<1.5 sec), and bounding pulses. Patients that have been adequately volume resuscitated but remain hypotensive and have clinical signs of vasodilation may benefit from vasopressor therapy (e.g., norepinephrine, vasopressin, or dopamine infusions). Currently one of the big controversies in human and veterinary critical care medicine is selecting which vasopressor should be used first. A recent state of the art review by Silverstein *et al* suggested the preferred initial vasopressor for humans with septic shock is norepinephrine followed by epinephrine and vasopressin. However, in veterinary medicine there is currently insufficient evidence to recommend a specific protocol.

SPECIFIC DRUGS

Dopamine

Dopamine may enhance renal and mesenteric perfusion at a dose of 1-4 mcg/kg/min IV CRI. At higher doses (~10 mcg/kg/min IV CRI), dopamine exerts predominantly beta-1 adrenergic effects to cause increased myocardial contractility. At even higher doses (~20 mcg/kg/min IV CRI), dopamine has predominantly alpha-adrenergic effects and will cause constriction of the renal arteries, thereby potentially reducing renal perfusion and causing irreversible renal damage.

Dobutamine

Dobutamine (2.5-10 mcg/kg/min IV CRI), a beta-1 agonist, increases cardiac output by enhancing myocardial contraction. One should use this medication with caution, as there are several potential serious adverse reactions, including generalized seizure activity and dysrhythmias.

Norepinephrine

Norepinephrine is a potent alpha-1 mediated vasoconstrictor and is usually reserved for severe, unresponsive hypotension at doses of 0.05-1 mcg/kg/min IV CRI. In humans, norepinephrine is frequently the vasopressor of choice in patients with septic shock.

Vasopressin

Vasopressin (0.01-0.05 units/kg/hr IV CRI) is a potent vasoconstrictor mediated by V1a receptors on the vascular endothelium. As catecholamine receptors are reportedly dysfunctional and/or down regulated in prolonged acidemia, use of vasopressin in patients whose metabolic acidosis is still present and/or severe may be more effective. Studies in humans have shown lower levels of endogenous vasopressin in patients with septic shock, and therefore may be chosen for blood pressure support in this specific patient population. Dermal necrolysis has been reported.

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Acute Pancreatitis: What Do We Really Know?

Christopher Byers, DVM, DACVECC, DACVIM (SAIM), CVJ

Pathophysiology

Acute pancreatitis is frequently described as having four phases: initial acinar damage, local pancreatic inflammation, systemic inflammation, and infection of the necrotic pancreas.

Phase 1: Acute pancreatitis is induced by several molecular mechanisms inside acinar cells that trigger and direct a normal enzymatic process against the pancreatic acini. Experimental studies indicate apical enzyme activation, pH reduction, hydrolases, and cytoskeletal disruption play a role in premature trypsinogen activation.

Phase 2: Local pancreatic inflammation is the hallmark characteristic of the second phase of acute pancreatitis. A myriad of pro-inflammatory cytokines is expressed to attract, activate, and sequestrate inflammatory cells within the pancreas. The severity of disease seems to be determined by the events occurring in this phase.

Phase 3: The third phase of acute pancreatitis is characterized by loss of localization of pancreatic inflammation, thus affecting distant organs. Serum levels of various cytokines correlate with disease severity, and systemic inflammatory response syndrome (SIRS) leading to multiple organ dysfunction syndrome (MODS) helps define morbidity and mortality for this disease.

Phase 4: The mechanism responsible for the progression of acute pancreatitis to necrotizing pancreatitis is not known. Infection that may lead to sepsis, and MODS has a significant impact on prognosis. Possible routes of infection are hematogenous, reflux from the duodenum, reflux of infected bile, direct transperitoneal spread, and translocation via intestinal lymphatics. Exact pathophysiological mechanisms remain unclear.

Etiology & Clinical Signs

No age, sex, or breed predisposition has been recognized in cats with acute pancreatitis. Furthermore, no relationship with body condition score (BCS) has been established. Frequently the underlying cause of pancreatitis in cats is unknown. Several risk factors have been documented, including concurrent disorders (inflammatory bowel disease, cholangiohepatitis, hepatic lipidosis), infections (feline infectious peritonitis, toxoplasmosis, *Amphimerus pseudofelineus, Eurytrema procyonis*, calicivirus, parvovirus, herpesvirus*),* trauma (surgery, high-rise syndrome), common bile duct obstruction, pancreatic neoplasia, bile or duodenal reflux, and some drugs (organophosphates).

The most common clinical signs are hyporexia/anorexia (63-100%) and lethargy (50-100%). Cats infrequently vomit (35-52%) and rarely manifest pyrexia (7%). Other reported clinical signs include dehydration (33-92%), PUPD (20%), diarrhea (11-15%), weight loss (33%), tachypnea (74%), hypothermia (68%), tachycardia (48%), abdominal discomfort (9-25%), icterus (16-64%) and dyspnea (20%). Approximately one quarter of cats will have a palpable abdominal mass, and this may be misdiagnosed as mesenteric lymphadenomegaly or associated with the intestinal tract.

Laboratory Testing

After obtaining a complete history and performing a thorough physical examination, the astute clinician should perform a logical series of initial tests that includes:

- Complete blood count (CBC): Common abnormalities include non-regenerative anemia, hemoconcentration, leukocytosis or leukopenia.
- Serum biochemical profile (CHEM): Common abnormalities include ionized hypocalcemia, elevated hepatocellular & cholestatic enzymes, hyperbilirubinemia, hypoalbuminemia, hyperglycemia, hypercholesterolemia, azotemia, hypokalemia. In one case series, 33% of cats had no abnormalities in their chemistry results.
- Urinalysis (UA): common abnormalities include variable specific gravity, proteinuria
- Serum pancreas-specific lipase
- Pancreatic fine needle aspiration and/or biopsy

Ancillary laboratory testing (i.e.: liver biopsy, cobalamin measurement, etc.) should be dictated by a patient's history and physical examination that may raise meaningful concerns for relatively common concurrent diseases (i.e.: cholangiohepatitis, inflammatory bowel disease, hepatic lipidosis).

Diagnostic Imaging
A variety of imaging modalities may be utilized for patients living with acute pancreatitis:

- Abdominal Radiography (AXR): Abdominal radiography is widely available, financially friendly, safe, and non-invasive. Furthermore, this modality is justified to rule out some causes of vague gastrointestinal signs. Roentgen signs of acute pancreatitis include loss of serosal detail in the cranial abdomen, increased angle between the pyloric antrum and proximal duodenum, left gastric displacement, right and/or ventral displacement of the descending duodenum, dilated hypomotile descending duodenum and caudal displacement of the transverse colon. These signs are commonly quite subtle, and as such, one may not make a conclusive diagnosis of acute pancreatitis based on AXR alone.

- Abdominal Ultrasonography (AUS): Compared to AXR, AUS is more sensitive and specific for diagnosing pancreatitis. A recent study evaluated 35 cats with clinical signs consistent with pancreatitis that had an abdominal ultrasound examination and fPLI measured within three days of AUS. Ultrasound characteristic associated with the highest sensitivity was hyperechoic peri-pancreatic fat (68%); increased pancreatic thickness, an abnormal pancreatic margin and hyperechoic peri-pancreatic fat were all associated with a specificity >90%. With an elevated fPLI, AUS had a sensitivity of 84% and specificity of 75%. Another study of 161 cats showed only fair agreement between fPLI and an ultrasonographic diagnosis of pancreatitis. Compared to AUS, endosonography (EUS) visualized pancreatic margins and parenchyma superiorly in all cats with pancreatitis compared to AUS. However, EUS findings did not alter the diagnosis of pancreatitis compared to AUS. Endosonography may be beneficial for patients where AUS fails due to obesity, hyperechoic mesentery or excessive intestinal gas.

- Computed Tomography (CT): The cornerstone of diagnosis of pancreatic diseases in people is CT. Contrast enhancement improves the accuracy of CT in humans and a correlation exists between the severity of CT pancreatic changes and disease severity. Head *et al* showed contrast enhancement in cats with pancreatitis was inhomogeneous and took ten minutes to peak while normal feline pancreas enhanced homogenously and peaked immediately. In a study to diagnose pancreatitis in cats, Forman *et al* compared helical CT with serologic testing and abdominal ultrasonography; CT was less sensitive and specific than AUS in diagnosing pancreatitis.

- Magnetic Resonance: Magnetic resonance imaging (MRI) and MR cholangiopancreatography (MRCP) has recently been evaluated in cats with pancreatitis. Ten cats with suspected pancreatitis were enrolled based on history, physical examination and appropriate diagnostic test results. Abnormalities detected via MRI included T1 pre-contrast hypointense and T2 hyperintense pancreas with a dilated pancreatic duct. Based on this study, MRI/MRCP may be beneficial for those patients with equivocal ultrasonographic findings.

Thoracocentesis / Peritoneocentesis
Pleural and/or peritoneal effusion is relatively common in cats with acute pancreatitis. Saunders *et al* documented pleural effusion in 29% of patients and peritoneal effusion in ~14% of cats with acute pancreatitis. Ferreri *et al* showed 28% incidence of peritoneal effusion in cats with acute necrotizing pancreatitis. Akol *et al* documented peritoneal effusion in all cats with pancreatitis and hepatic lipidosis.

Treatment & Monitoring
Treatment of acute pancreatitis is aimed at correcting any underlying predisposing factors and reducing pancreatic inflammation. As supportive therapy remains the mainstay of therapy for feline acute pancreatitis, adherence to Kirby's Rule of 20 will afford a logical means of intervening for patients and will help guide therapies and monitoring. Adequate pain control requires the use of opioids, commonly pure mu opioids provided via constant rate infusions (CRIs). Meperidine may be favored over morphine, as human studies showed morphine caused an increase in sphincter of Oddi pressure. There is no clinical evidence to suggest morphine aggravates or causes pancreatitis or cholecystitis in cats. A multimodal approach to analgesia is recommended, and common adjuncts include a ketamine intravenous CRI, gabapentin, epidural catheters, and intra-peritoneal local anesthetic infusion.

The routine use of antimicrobials in patients with pancreatitis remains controversial. The occurrence of pancreatic infection is a leading cause of morbidity and mortality in acute necrotizing pancreatitis in humans. The organisms are predominantly gut-derived, and the majority of infections are monomicrobial in nature. Simpson *et al* identified 35% of cats with moderate-to-severe pancreatitis had bacterial infections, most prevalent in those with necrotizing or suppurative severe acute pancreatitis. The localization and intra-pancreatic bacteria suggested translocation of enteric bacteria as the likely source of infection. Given the incidence of nausea and paralytic ileus, a multimodal approach to antiemetic therapy may be beneficial. $5HT_3$ antagonists (dolasetron, ondansetron) and alpha-2 adrenergic antagonists (chlorpromazine) are very effective antiemetic agents. Maropitant, an NK_1 antagonist, is very

effective in controlling nausea, and may confer additional beneficial anti-inflammatory and analgesic effects through substance P modulation. Experimental feline models have demonstrated that dopamine reduced pancreatic microvascular permeability and improved pancreatic blood flow. Thus, the use of metoclopramide, a dopamine antagonist, is cautioned for cats with acute pancreatitis.

Nutritional support is of paramount importance for maximizing a successful outcome and should be implemented as soon as possible. Prolonged fasting (>3 days) to avoid pancreatic stimulation only serves to compound malnutrition. Few reasons (dehydration, hypotension, hypothermia, electrolyte imbalance, glucose abnormalities, acid-base derangements, inability to protect airway, need for sedation/anesthesia) exist to justify withholding nutrition from a pancreatitis patient; once these issues have been addressed, nutritional support should be instituted immediately. Enteral support is preferred to parenteral administration, but the latter may be necessary when feeding the gastrointestinal tract is not feasible. Placement of a temporary supplemental feeding tube to provide early enteral nutrition should be considered a mandatory aspect of effective treatment. Klaus *et al* evaluated 55 cats with suspected acute pancreatitis that received either bolused feeding or constant infusion via nasogastric tubes; all tolerated feedings and complications were minor (mechanical – 13%; diarrhea – 25%; vomiting after placement – 20%; vomiting after feeding – 13%). Force/coax feeding is not recommended due to the possibility of promoting food aversion. Administration of liquid diets with >25% calories as protein and fat, as well as feeding "maintenance" food, has not been associated with overt adverse events. Jejunostomy tubes and/or parenteral nutrition should be used in patients with refractory vomiting. Parenteral cobalamin supplementation should be provided to those with low or low-normal levels.

Canine patients with acute pancreatitis have reduced alpha-2 macroglobulin levels associated with increased mortality. Given fresh frozen plasma (FFP) contains alpha-2 macroglobulin, treatment with this fluid may be beneficial. Alpha-2 macroglobulin levels have not been investigated in cats with acute pancreatitis, but anecdotally FFP is believed to be useful in cats with severe acute pancreatitis. Patients for whom lymphoplasmacytic infiltration has been documented within the pancreas may benefit from anti-inflammatory corticosteroid therapy; further investigation regarding this issue is needed. Experimental models have shown dopamine improved pancreatic blood flow and reduced microvascular permeability when administered up to 12 hours after induction of acute feline pancreatitis. Increases of both histamine and bradykinin have been associated with development of hemorrhagic necrosis in experimental feline pancreatitis. The clinical utility of dopamine infusion and histamine antagonism has not yet been properly investigated. Some have advocated peritoneal lavage with subsequent infusion of local anesthesia. The peritoneal cavity is infused with 10-20 mL/kg of warmed 0.9% NaCl and subsequently drained; this process is repeated 3-4 times, and after the last drainage, diluted bupivacaine (2 mg/kg) is infused.

Prognosis

Prognosis is typically variable for cats with acute pancreatitis. Kimmel *et al* showed severe ionized hypocalcemia (iCa^{2+} ≤1.00 mmol/L) was associated with a poor prognosis. Stockhaus *et al* showed dyspnea, hyperkalemia (>5.5 mmol/L) and fPLI >20 ug/L at time of hospital admission were significantly associated with an adverse outcome. Acute pancreatitis may be associated with transient or permanent diabetes mellitus. Potential life-threatening complications include disseminated intravascular coagulation (DIC), thromboembolism, dysrhythmias, sepsis, acute kidney injury (AKI), pleural effusion and pulmonary edema.

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5th WORLD FELINE VETERINARY CONFERENCE

Complex Disease Management

Exploring Feline Comorbidities

Oct. 31 – Nov. 3, 2019
Hilton San Francisco
Union Square
San Francisco, CA

FRIDAY, NOVEMBER 1, 2019

TIME	SESSION TITLE	SPEAKER	ROOM	SPONSOR/ PARTNER
6:00 - 7:00 am	Early Riser Yoga Class*		Franciscan C&D	
7:15 - 8:00 am	Continental Breakfast		Continental Ballroom Foyer	
8:00 - 8:15 am	President's Address	Dr. Apryl Steele	Continental Ballroom 1-6	
8:15 - 8:25 am	JFMS 20th Anniversary Award	Dr. Margie Scherk	Continental Ballroom 1-6	
8:25 - 9:05 am	Why Are Comorbidities the "New" Norm for Cats?	Dr. Margie Scherk	Continental Ballroom 1-6	Pro Plan Veterinary Diets
	Practice Management: Work Life Balance & Making Time for Yourself	Ms. Melissa Tompkins	Continental Ballroom 7	VHMA
9:10 - 10:00 am	Comorbidities in Retrovirus Infected Cats	Dr. Michael Lappin	Continental Ballroom 1-6	Pro Plan Veterinary Diets
	Practice Management: What Do You Do When a Client Says No?	Ms. Melissa Tompkins	Continental Ballroom 7	VHMA
10:00 - 11:10 am	Networking Refreshment Break		Exhibit Hall	
11:10 - 12:00 pm	Managing Feline Endocrine Diseases: Easier Said Than Done	Dr. Audra Fenimore	Continental Ballroom 1-4	Boehringer Ingelheim
	What Makes a GI Pathogen, Pathogenic?	Dr. Michael Lappin	Continental Ballroom 5-6	Pro Plan Veterinary Diets
	Practice Management: Impact of Environmental Design & Choices on the Cat	Dr. Ragen McGowan	Continental Ballroom 7	Pro Plan Veterinary Diets
12:00 - 1:30 pm	Lunch		Exhibit Hall	
12:15 - 1:15 pm	Lunch & Learn #1:* Feline Infectious Respiratory Disease: What Every Veterinarian Should Know	Dr. Annette Litster	Imperial Ballroom A	zoetis
12:15 - 1:15 pm	*Lunch & Learn #2:** It's a New World: Update on Feline Retrovirus Testing	Dr. Susan Little	Imperial Ballroom B	IDEXX
12:15 - 1:15 pm	*Lunch & Learn #3:** Maintain Muscle Mass While Feeding Feline Renal Therapeutic Diets	Dr. Amy Farcas	Yosemite	Royal Canin
1:30 - 2:20 pm	Chronic Enteropathy in Cats With Triaditis: Optimization of Diagnosis & Management	Dr. Stanley Marks	Continental Ballroom 1-4	Nutramax
	Setting the Stage: Managing CKD	Dr. Jessica Quimby	Continental Ballroom 5-6	KindredBio, WSAVA
	Practice Management: Feline Professional Liability Risk Management	Dr. Linda Ellis	Continental Ballroom 7	AVMA | PLIT
2:25 - 3:15 pm	New Insights in Hepatic Disease Associated With Triaditis	Dr. Stanley Marks	Continental Ballroom 1-4	Nutramax
	The Cushingoid Diabetic: Recognition, Diagnosis, & Management	Dr. Audrey Cook	Continental Ballroom 5-6	Royal Canin
	Practice Management: Does Cat Friendly Practice® Impact Your Team's Risk of Injury?	Mr. Scott Simpson	Continental Ballroom 7	AVMA | PLIT
3:15 - 4:00 pm	Networking Refreshment Break		Exhibit Hall	Elanco
4:00 - 4:50 pm	Lessons Learned: Diagnosis & Management of Exocrine Pancreatic Disorders in Cats With Triaditis	Dr. Stanley Marks	Continental Ballroom 1-4	Nutramax
	Managing IBD in the Diabetic Cat - Part 1: Challenges	Drs. Audrey Cook & Amy Farcas	Continental Ballroom 5-6	Royal Canin
	Practice Management: Incorporating Feline-Friendly Techniques into Practice Management Decisions	Ms. Melissa Tompkins	Continental Ballroom 7	VHMA
4:55 - 5:45 pm	How Chronic Disease Affects Pain Perception & Management	Dr. Elizabeth Colleran	Continental Ballroom 1-4	Assisi Animal Health
	Managing IBD in the Diabetic Cat - Part 2: Strategies	Drs. Audrey Cook & Amy Farcas	Continental Ballroom 5-6	Royal Canin
	Practice Management: Team Building: Create Stronger Practice Teams	Ms. Melissa Tompkins	Continental Ballroom 7	VHMA
	Student Forum: Feline Education *(students-only)*		Imperial Ballroom A	Pro Plan Veterinary Diets
5:45 - 6:45 pm	Happy Hour Reception		Exhibit Hall	Mirataz (mirtazapine transdermal ointment)

*Separate Registration Required. No fees associated.

Why Are Comorbidities the "New" Norm for Cats?

Margie Scherk, DVM, DAVBP (Feline)

Introduction

The observation that comorbidities are seen frequently in cats is not, unto itself, surprising. Cats are living longer than ever, and things "wear out" over time. But is this a new problem? Perhaps we are simply recognizing comorbidities because we are screening/looking for problems before they become clinically evident. Yet, some conditions, for example hyperthyroidism (Peterson), diabetes (Prahl), and CKD (Lefebvre, Lulich, Reynolds, Ross), are actually becoming more common.

What Mechanisms May Cause Comorbidities?

As with any other species, over time, oxidative stress from normal, or enhanced, wear-and-tear results in cellular injury or death through complex free radical pathways. Free radicals are by-products of normal metabolism such as mitochondrial cellular respiration, phagocytosis, digestion, and inflammation. Additionally, they are formed by exogenous agents, including drugs, xenobiotics (chemicals found in an organism not normally produced or expected to be present in it, e.g., smoke, fire retardants) and ionizing radiation (including that from the sun). If the cell's ability to neutralize free radicals is exceeded, permanent damage occurs and results in DNA damage, cell injury, inflammation, fibrosis, cell death or the inability to reverse neoplastic transformation. Free radicals are balanced by endogenous antioxidant systems and their neutralization by these mechanisms contributes to the outcome for the patient. (Mandeleker)

Anecdotally, some claim that cats are a species prone to inflammation. Lymphocytes and plasma cells are arguably the most common cellular infiltrates in cats suggesting chronic antigenic stimulation. In small doses, inflammation is protective; chronically, however, it can be detrimental with inflamed tissues possibly even undergoing malignant transformation as it is currently believed to be the case with IBD transforming to small cell alimentary lymphoma. (Morrison)

Might infectious agents play a role in comorbidities? Could recrudescence of regressive Feline Leukemia virus (FeLV) or loss of cell mediated immune control of Feline Infectious Peritonitis (FIP) (e.g., dry renal FIP) contribute to this phenomenon of developing comorbidities? At the present time, there is no evidence for this, but any significant disease could allow reactivation (FeLV) or suppression of cell mediated immunity (FIP).

We know little about the feline immune system specifically. Could a compromised immune system result in disease beyond infection? (Singer) We speculate on immunosenescence in cats, but this is mostly extrapolated from research in other species. (Scherk) Similarly, many of our beliefs regarding physiology and pathophysiology, along with therapy (including nutrition) are extrapolated.

It is reasonable, from a traditional pathophysiologic approach to look for direct underlying mechanisms, such as the role of ischemia in the development of CKD (Brown) or the interesting studies looking at the effects of Crandall Rees feline kidney (CRFK) cell antibodies associated with vaccination on the development of CKD. (Lappin, Whittemore, Finch, Conroy)

Cats are intriguing. In the more studied canine, finding hyperthyroidism coexisting with diabetes mellitus (DM) is rare. Of course, hyperthyroidism is far more common in cats, but none-the-less, these two conditions are not infrequently seen together in this species. Similarly, diabetes is seen with any chronic inflammatory disease, including (but not only) pancreatitis. Chronic kidney disease (CKD) is also commonly unmasked or already present in cats with hyperthyroidism. Cardiac changes are seen with hyperthyroidism. Degenerative joint disease (DJD) may be present in any cat with any disorder, and concurrence between CKD and DJD has been noted. (Marino) Interestingly, a relationship has been suggested between fractured patellae in cats with retained deciduous teeth ("knees and teeth syndrome"). (Langley-Hobbs) An association between periodontal disease (PD) and the risk of developing CKD has been verified: cats with Stage 3 or 4 PD have greatest risk for developing CKD. While these are also the oldest cats, a relationship between the two conditions is made more likely, however, given that the Trevejo study included 169,242 cats. Obesity has been shown to be associated with DJD, DM, cardiac disease, respiratory illness, and other diseases. Since obesity is seen in 11.5% to 63% of pet cats, this has significant impact. (Scarlett 1994, Tarkosova) Unfortunately, as reported by Campigotto, only 9,886,899 of 19,015,888 cats even had one body weight measurement in their medical record. Asthma, idiopathic inflammatory bowel disease (IBD), pancreatitis, cholangitis, cholycystitis, triaditis, idiopathic cystitis (IC), and even dermatologic conditions are seen more commonly in cats housed strictly indoors. (Buffington 2002)

A shortlist of speculated pairings is shown in Table 1. Some of these may not have direct relationships and may be coincidental. Many studies consist of only small numbers of cats, so the power is insufficient to draw solid conclusions with some of these combinations.

Table 1. Comorbidity combinations recognized
Chronic kidney disease (CKD) + hyperthyroidism
CKD + degenerative joint disease (DJD) (Marino)
CKD + heart failure (Belanger)
CKD + periodontal disease (PD) (Trevejo, Finch)
Hyperthyroidism + diabetes mellitus (DM) (Hoenig p 1101)
DM + obesity (Hoenig p 1103)
DM + CKD (Perez-Lopez)
DM + lower urinary tract disorders (Greco)
DM + urinary tract infections + hyperthyroidism + CKD (Mayer-Roenne)
Obesity + DJD/DM/cardiac disease/respiratory illness (Scarlett 1994, Tarkosova)
Triaditis (Simpson)
Hypertension + hyperthyroidism
Hypertension + CKD
Hypertension + hyperaldosteronism
Knees and teeth syndrome (Langley-Hobbs)
CKD + thin body condition/ PD/cystitis (Greene)
Underweight + DJD/DM/CKD/hyperthyroidism/neoplasia (Saito, Campigotto)

It's Become Complicated: More Than Physical
Apart from the mechanics of cells and pathology, recent focus in some arenas of human medicine has been towards complex diseases rather than simply organ-specific disease. Since the 1800s, medicine has been based in the understanding of physiology with cause and effect and Koch's postulates to explain the development of disease. It has enabled us to create tools for the diagnosis and treatment of illness. Science is a way of thinking and approaching a problem, however, so new concepts arise. Incorporating an understanding of cellular communication through immunologic defense mechanisms improved the field of biomedicine. (Kirkengen) The body can be viewed as being more integrated rather than system-restricted.

Cats appear to be similar to human patients with chronic complex disease states. Fleshner states that: "The disparity between physical and psychological stressors is an illusion. Host defence mechanisms respond in adaptive and meaningful ways to both." In humans, the term "complex diseases" is used to describe the coexistence of conditions, such as Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) with other syndromes, such as those of chronic pain, Chronic Fatigue Syndrome (CFS) or Irritable Bowel Syndrome (IBS). (Kirkengen) This is analagous to the complex Buffington has called "Pandora Syndrome" in cats. (Buffington 2014) The fact that unrelated organ systems are affected negatively within the same individual is thought to be due to psychoneuroimmunology, the complex interrelationship between the mind, the immune and neurologic systems, all ultimately manifesting as disease in disparate body systems. In Pandora Syndrome, Buffington describes a similar interrelatedness of genetics, the fetal environment (i.e., the effects of stress on the queen), and creating a susceptible individual who, when placed in a provocative situation or environment, may become sick. This is not an easy disease model to test as we don't know what to measure. (Buffington 2014)

Any organism that feels threatened, whether the threat is real or speculative, has hormonal, neurological and immunological responses. If these responses remain activated or are reactivated repeatedly, it becomes that being's new norm. Some individuals respond more benignly than others in whom the emotional, psychological and physiological state will result in a negative or diseased state. Lifestyle, environment, and experiences all play important roles as well as those of the mother (or queen) while the fetus was *in utero*. Does this say something about how cats experience life? With us?

Re-evaluating what we believe we know
While we recognize more combinations of diseases, we must also continue to challenge what we believe we understand. New findings are showing us that even within the traditional bioscience perspective, we may need to re-evaluate our beliefs. McLeland has shown that the histologic changes we associate with CKD, occur in cats without clinical or laboratory evidence of CKD. In fact, renal aging in cats *without* CKD is characterized by increasing glomerulosclerosis, tubular atrophy, interstitial inflammation, fibrosis and fibrointimal hyperplasia.

The etiology of hyperthyroidism is multifactorial. (Peterson) Not only is there evidence for environmental and nutritional factors contributing to hyperthyroidism, we now have evidence that cats exposed to higher levels of the flame retardant tris(1,3-dichlor- oisopropyl) phosphate have significantly higher prevalence of hyperthyroidism. Previously suggested to contribute to this condition, PBDE flame retardants have been phased out due to concerns of persistence, bioaccumulation, and the potential to cause adverse health effects. (Poutasse) Exposure to these substances, as well as other agents may partly explain why cats housed only indoors have a higher prevalence of hyperthyroidism than cats with outdoor access. (Buffington 2002)

We have become aware of the importance of meeting not just the environmental, but also behavioural needs of cats for health. This applies to all cats regardless of their living arrangement, but clearly the cat that has less control over choosing when and what they are exposed to, is in a more provocative situation - one that may result in engaging the complex psychoneuroimmunologic mechanisms that result in dis-ease. (Stella)

However, it might be worth considering whether other aspects of the safe indoor lifestyle may play a role in not just increasing the prevalence of hyperthyroidism, but also the other conditions already mentioned.

- A monotonous and overly predictable environment is stressful. (Buffington 2006) Cats may not be able to perform species typical behaviours that express their cat-like nature. In addition to increased prevalence of diseases, this psychological and physiological stress that may result in problem behaviours – unwelcome but natural behaviours, e.g., spraying or scratching -, behavior problems (e.g., obsessive grooming) or physical illness.
- Signs of stress and anxiety may be overt (e.g., changes in appetite, grooming, increased vocalization, hiding, vigilance, aggression, spraying or compulsive behaviours), or subtle (e.g., decreased activity, play, exploratory behavior/inquisitiveness, facial marking, affiliative interactions with people and other animals). (Amat)
- Buffington (2006) collated evidence from multiple studies showing that lower urinary tract diseases (idiopathic and calcium oxalate urolithiasis), (unsurprisingly) obesity and, interestingly, even dental resorptive lesions were found to be associated with indoor living. In fact, indoor and city living, had odds ratios of 4.5 and 4.4, respectively for dental lesions. (Scarlett 1999)
- Indoor confinement and physical inactivity are risk factors for developing DM. (Slingerland)

What, if anything, can we do about this new norm of comorbidities?

1. Screen healthy cats for insipient disease. (Paepe) Often sequential assessments will provide earlier identification of a problem (e.g., weight loss, changes in body condition score [BCS], muscle condition score [MCS}, blood pressure, creatinine, etc.) before the values fall outside the normal reference interval.
2. Be selective. Consider the prevalence not only within the region but also age of the patient. Similar to vaccination, where the goal is to perform risk assessment of the individual, not every patient needs a comprehensive “minimum” database.
3. Be cognisant of the limitations of every test.
4. Weigh, BCS, MCS cats at every visit. Serial changes (e.g., percentage weight change) are much more meaningful than absolute numbers or scores. Blood pressure should be measured in all cats over 3 years of age as elevations suggest conditions that should be further assessed. (Taylor)
5. Nutritional intervention should be considered and implemented early. It may help modulate the impact of free radical damage. (Cupp 2008) It definitely can benefit an older cat by preventing or slowing muscle loss. Numerous studies have shown the risks of sarcopenia in the older cat, contributing to the development and progression of comorbidities. Sarcopenia results in poorer response to treatment, poorer quality of life as well as decreasing response to therapy and reduced survival in CKD, heart disease, lymphoma and other cancers. (Cupp 2010, Doria-Rose, Boyd, Freeman 2012, 2016, Finn, Krick)
6. Promote overall good health, including dental health regardless of age.
7. Become informed about the physical and social home environment. (Buffington Captivity) Teach the client about meeting environmental and behavioural needs and what signs may indicate stress in their cat. Rather than merely coping and surviving, an enjoyable, interesting and stimulating environment will improve the chance of good health outcomes.
8. Optimize hydration through attention to desirable water resources (wide, clean bowls, fresh water in easily accessible locations). Ensure that litter boxes are pleasant: clean, easy to access and enter/exit, filled with the right depth of the litter the individual cat likes.
9. Last, but certainly not in importance, provide analgesia. Be suspicious of hidden pain or discomfort. Look for, and counsel the client on, the subtle changes that may indicate that pain is present.

Summary
With such a plethora of combinations of diseases existing, it appears that comorbidities are the new norm for cats. Why conditions present concurrently and what the mechanisms for this is not known. Perhaps serious consideration needs to be given to an integrated view of health rather than a purely biomechanical one. Future thinking and research will be interesting, and results will hopefully benefit cats as well as other species.

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Line Antigens, α-Enolase, and Annexin A2 in Vaccinated and CRFK Hyperinoculated Cats. J Vet Intern Med. 2010 Mar;24(2):306-13.

NOTES:

Comorbidities in Retrovirus Infected Cats

Michael Lappin, DVM, PhD, DACVIM

Introduction

Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are retroviruses associated with the development of immunodeficiency. FeLV is in the subfamily Oncovirinae; FIV is in the subfamily Lentivirinae. The retrovirus status of all cats should be known and excellent reviews on both organisms are available.[1-3] The feline foamy virus is another retrovirus and may be associated with clinical disease in some cats.[4]

The clinical manifestations of FeLV and FIV infections of cats are diverse and include fever, weight loss, anemia, neurologic signs, lymphadenomegaly, oral cavity inflammation, upper respiratory disease, lower respiratory disease, reproductive disease, intraocular inflammation, dermatologic disease, urinary tract disease, and gastrointestinal tract disease. Clinicians must be careful not to ascribe all clinical diseases in retrovirus-seropositive cats to the virus; many times the clinical signs are due to secondary infections with primary treatments. The secondary infection may or may not be potentiated by immunodeficiency induced by the retroviral infection.

Immunodeficiency syndromes related to FeLV occur secondary to T lymphocyte depletion (both CD4+ and CD8+ lymphocytes) or dysfunction and either neutropenia or neutrophil function deficit. The envelope protein p15e of FeLV is associated with the development of immunosuppression. Some cats with latent infection also have evidence of immunosuppression. Strains of FeLV that rapidly induce immunodeficiency syndromes in cats have been isolated and cloned. Most naturally infected, persistently viremic cats with FeLV infection will have clinical signs of disease within 3 years.

FIV has been documented to replicate in a number of cells including T-lymphocytes (CD4+ and CD8+), B-lymphocytes, macrophages, and astrocytes. Following the primary phase of infection, a subclinical, latent period of variable length develops. The duration of the latent period is related in part to the strain of virus and the age of the animal when infected. The first strain of FIV isolated, the Petaluma strain, induces laboratory evidence of immuno¬deficiency within 14 months following infection. However, cats experimentally infected with this strain of virus have remained clinically normal for years after primary infection. The median age of healthy naturally infected cats and clinically ill naturally infected cats are approximately 3 years and 10 years, respectively, suggesting a latent period of years for most strains of FIV. Chronic experimental and naturally occurring infection results in a slow decline in CD4+ lymphocytes numbers and lymphocyte response to mitogens as well as decreased production of interleukin 2. Humoral immune responses, neutrophil function, and natural killer cell function are also effected. What stimulates the induction of the immune deficiency stage of FIV infection is currently unknown; coinfection with *Mycoplasma hemofelis*, *T. gondii*, feline herpesvirus 1, and feline calicivirus as well as immunization failed to potentiate FIV-associated immunodeficiency. Coinfection with FeLV potentiates the primary and immune deficiency phases of FIV and results in a greater chance for clinical disease than infection by either agent alone. Recently, gammaherpesvirus (FcaGHV1) has been detected in cats.[5-8] Cats coinfected with FIV and FcaGHV1 infections shed more FcaGHV1 than cats without FIV infection. Potential disease associations are currently being explored.

Unfortunately, a positive FeLV or FIV serologic test does not correlate directly to immunodeficiency. While coinfection of FeLV and FIV seropositive cats with other infectious agents is common, most infections also occur in seronegative cats and do not require immunosuppression to induce disease. Table 1 is a list of the clinical syndromes associated with primary viral infection and secondary infectious agents commonly recognized in retrovirus-infected cats.[9-22]

Management of opportunistic infections in retrovirus-infected cats. Following the confirmation of a retroviral infection in an individual cat, the owner should be counseled on potential zoonotic risks and management of chronic retroviral infections. If the owner chooses to continue managing the case, further diagnostic testing for opportunistic agents potentially associated with the presenting clinical syndromes should be performed. While it appears unlikely the feline retroviruses will infect people,[23] immunosuppressed cats may be more likely than healthy cats to shed other zoonotic agents into the environment. This is particularly true of the enteric pathogens.

Clinical syndromes associated with retroviral infections in cats and possible opportunistic agents

Clinical syndrome	Agents
Stomatitis	Calicivirus; bacterial flora overgrowth; candidiasis
Diarrhea*	*Cryptospori¬dium* spp.; *Cystoisospora* spp.; *Giardia* spp.; *Salmonella* spp.; *Campylobacter* spp.; helminths; *Tritrichomonas* spp.
Upper respiratory tract	Feline herpesvirus 1; overgrowth of bacterial flora; *Cryptococcus* spp,; caliciviruses
Pyothorax	Bacterial
Pneumonia/pneumonitis	Bacterial; *Toxoplasma gondii*; *Cryptococcus* spp.
Dermatologic/otitis externa	Bacterial; atypical *Mycobacteri¬um*; *Otodectes cynotis*; *Demodex cati; Notoedres cati*; dermatophytosis; *Cryptococcus* spp.; coxpox
Hematologic*	Hemoplasmas; *Bartonella* spp., FeLV
Hepatic*	*T. gondii*; feline infectious peritonitis virus; bacterial
Neurologic*	*T. gondii*; *Cryptococcus* spp.; feline infectious peritonitis virus; FeLV
Urinary tract infection	Bacterial
Glomerulonephritis*	Bacterial; feline infectious peritonitis virus
Renal failure*	Bacterial; feline infectious peritonitis virus
Ocular*	*T. gondii*; feline infectious peritonitis virus; mycotic, particularly *Cryptococcus* spp.

*Syndrome also associated primarily with the retroviruses

Due to the lack of routine availability of immune function testing, it is often difficult to determine the prognosis for a retrovirus-seropositive cat concurrently infected with another infectious agent. Since retrovirus serologic tests do not prove immunodeficiency and many of the opportunistic agents also induce disease in immunocompetent cats, response to treatment in the individual cat is the only way to determine prognosis. Treatment should be instituted for the potential opportunistic agent using standard protocols. In general, the upper dosage range for anti-microbial agents should be used and treatment should be continued longer than in immunocompetent cats since retrovirus-induced immunodeficiency may be present.

Use of antiviral drugs and immune modulating substances to attempt to improve the clinical signs of illness in retrovirus infected cats have had variable success.[1-3, 24-29]

Immunosuppressed cats should be housed indoors to avoid infecting other cats and to avoid contracting opportunistic infections. In general, modified live vaccinations should be avoided. Stress should be minimized and the cat should be fed a high quality diet.

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NOTES:

Managing Feline Endocrine Diseases: Easier Said Than Done

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Introduction

This lecture will be case-based, working through challenging feline diabetic cases.

Diabetes Mellitus (DM) is a common endocrine disease in cats characterized by PU/PD, weight loss, and persistent hyperglycemia.

Unlike dogs, cats develop type 2 DM which is characterized by insulin resistance and impaired insulin secretion. Causes of insulin resistance in cats include genetics, obesity, and certain drugs such as glucocorticoids. A study evaluating the risk factors for developing DM in cats revealed that Tonkinese, Norwegian Forest, and Burmese cats had increased odds for developing DM compared to crossbred cats. This study also found that cats with increasing body weight (greater than 4.0 kg) also had increased odds of developing DM.[1] Insulin secretion can also be impaired from loss of pancreatic B cells from release of inflammatory adipokines (pancreatitis, neoplasia), chronic hyperglycemia (glucose toxicity), and obesity.

The goals of diabetic management are to resolve diabetic clinical signs and attain euglycemia while avoiding hypoglycemia, and if diagnosed in the early stages, remission. Managing diabetes can involve a multimodal approach.

Diabetic remission is defined as achieving euglycemia for at least 4 weeks without insulin administration and the absence of diabetic clinical signs. Diabetic remission can be dependent on a number of factors including initial aggressive glycemic control, the implementation of longer acting insulins, and the underlying trigger of feline diabetes. In many cats, remission can be attained 4-6 months into therapy but reports of approximately 25% of cats will come out of remission and be dependent on insulin therapy. If a patient can achieve remission, the duration of remission can be variable. Unfortunately, if a hyperglycemic state persists (approximately greater than 2 months), chances of remission are decreased.

Diet is an important component of diabetic management. There is strong evidence that a high-protein, low-carbohydrate diet can lower postprandial hyperglycemia to then help resolve glucose toxicity, promote weight loss and maintain muscle mass. A study performed by Farrow et al. in 2013 determined that feeding a high carbohydrate diet to lean, non-diabetic cats (approximately 50% energy from carbohydrates) resulted in higher postprandial glucose concentrations for a median of 24 hours compared to cats fed a higher protein, higher fat diet.[2] Another study revealed significantly higher diabetic remission rates (68% to 41%) in cats fed a low carbohydrate diet (12% energy from carbohydrates) compared to cats fed a higher carbohydrate diet (26% energy from carbohydrates). [3]

Incretins are gastrointestinal hormones that play an integral role in halting gluconeogenesis, releasing insulin from the pancreas, and suppressing the appetite. In cats, high protein and fat tend to stimulate incretins whereas in humans and in dogs, incretins are stimulated by carbohydrates. Such a response in cats support a low carbohydrate diet in the treatment of feline diabetes. Diet also plays a crucial role in maintaining ideal body weight to increase insulin sensitivity. Physical activity is likely of benefit in cats as it has been shown to be in people with type 2 DM.

Insulin therapy is the mainstay treatment for cats with diabetes. A number of insulins are available for feline diabetic regulation. Failure to initiate insulin therapy early on in the course of disease may determine whether or not diabetic remission is feasible.

A few insulins are available for the treatment of feline DM include ProZinc insulin (recombinant PZI; Boehringer Ingelheim Animal Health), Vetsulin (Merck Animal Health), Lantus (Sanofi Aventis), and Levimir (Novo Nordisk) with the longer acting insulins being the treatment of choice in the diabetic cat.[4] Although any insulin has the ability to achieve diabetic remission, longer acting insulins have been shown to increase the success of diabetic remission and lower mean daily glucose concentrations in diabetic cats.[5-7]

If a cat is intolerant to insulin therapy, oral hypoglycemic agents may be of benefit. Oral hypoglycemic drugs act to promote secretion of insulin from B cells, help increase insulin sensitivity, or decrease glucose absorption from the GI tract. Glipizide and acarbose are two oral hypoglycemic medications that have been traditionally used in cats with DM. A thiazolidinedione, such as pioglitazone used in humans with type 2 DM was studied in a group of diabetic cats. Results revealed that this drug may be another safe and efficacious option in enhancing insulin sensitivity and lipid metabolism in cats with diabetes.[8]

Newly diagnosed diabetic cats can have a good prognosis. A recent study performed involving 185 client-owned diabetic cats revealed a median survival time of 1488 days. Factors found to increase survival time included a low carbohydrate diet, occurrence of remission, lack of DKA at the time of diagnosis, and lower mean glucose levels during treatment.[9]

This lecture will be case-based, working through feline hyperthyroidism cases.

Background

Feline hyperthyroidism is the most common endocrine disorder in cats typically characterized by benign functional hyperplasia or by a functional adenoma causing excessive thyroid hormone production. Thyroid carcinomas are rare and account for approximately 1-2 % of hyperthyroid cases.[1]

The exact etiology for hyperthyroidism is not completely understood however several hypotheses have been suspected including overexpression of the oncogene c-RAS which is present in those patients with adenomatous hyperplasia/thyroid adenomas, and environmental exposures including polybrominated diphenyl ethers (PBDEs). [2, 3] Despite these hypothesized etiologies, a single causal factor has yet to be identified.

Clinical signs associated with this syndrome include PU/PD, polyphagia, hyperactivity, vocalization, and GI symptoms including vomiting, diarrhea, and weight loss. Approximately 10% of hyperthyroid cats may have apathetic hyperthyroidism characterized by lethargy and anorexia. Physical exam findings may include a palpable goiter, heart murmur and/or arrhythmia and matted hair coat.[4]

Blood work abnormalities may include polycythemia, elevated liver values, azotemia, and hypocobalaminemia.

Feline hypertension is another clinical consequence associated with hyperthyroidism and can have detrimental effects on the body if uncontrolled. Target organ damage to the brain, retinas, kidneys, and heart are of concern resulting in CNS ischemia/infarction, retinal detachment and hemorrhage, glomerular hypertension, and compensatory cardiomyopathy.

Although treating feline hyperthyroidism can resolve its associated hypertension, additional therapies (as mentioned below) can be implemented to more quickly control hypertension.

Diagnosing Feline Hyperthyroidism

Serum thyroxine (TT4) is an excellent screening tool for diagnosing hyperthyroidism. With a sensitivity of 90%[5]; if within normal range or border-line positive with a clinical suspicion for hyperthyroidism, a free T4 could be performed. Although sensitivity is excellent with the fT4, 20% of cats who are euthyroid sick will have an elevated fT4 making specificity poor.[5]

If both TT4 and fT4 levels are within normal range and yet hyperthyroidism is still suspected, a T3 suppression test could be performed. T3 is administered at 25 µg/cat PO q 8 hrs. for 7 doses. T3 and T4 levels are measured 4-6 hours after the last treatment. Euthyroid cats have T4 suppression >50% baseline or <2 µg/dL. Hyperthyroid cats do not suppress. Equivocal test results and owner compliance can be an issue.

Peterson et al have evaluated the canine TSH assay to help diagnose feline hyperthyroidism. This assay appeared to be highly sensitive with 98% of hyperthyroid cats having undetectable/suppressed TSH levels. If a patient has a high-end of normal T4, high fT4, and undetectable TSH levels, such can be indicative of early hyperthyroidism.[6]

Thyroid scintigraphy using Technitium-99m can be helpful in visualizing uptake of the isotope at the level of the hyperfunctioning thyroid tissue. This imaging modality can be helpful in understanding unilateral vs bilateral vs ectopic disease.[1]

Treatment

A number of treatments exist for feline hyperthyroidism:

1. Antithyroid medications: Methimazole is the most commonly administered antithyroid medication to treat hyperthyroidism. It is a thioureylene drug that inhibits thyroid peroxidase-catalyzed reactions.[7] Carbimazole is another oral option which gets directly converted to methimazole after oral administration. Because these medications do not directly impact the thyroid nodule itself, most cats require higher doses of medication over time.
2. Side effects associated with these medications can occur within the first few months of administration including blood dyscrasias, GI upset, facial excoriations, and hepatopathies.
3. A transdermal methimazole preparation is available to help avoid GI side effects. Once to twice daily dosing can be as efficacious as the oral preparations.[8]
4. Dietary management: A restricted iodine diet may be helpful in controlling feline hyperthyroidism.
5. Hill's y/d® is a prescription diet that has an iodine content of ≤0.3 ppm and is available in dry or canned form. When fed an iodine-restricted diet, 42% of cats had serum TT4 levels within the reference range by 60 days and

83% of cats having normal TT4 levels by day 180.[9] Even cats experiencing moderate to severely elevated TT4 levels when followed 1 year after diet initiation can experience improved thyroid levels. [10]Reasons for unsuccessful treatment to include palatability and the patient's willingness to consume the diet, the addition of other foods containing higher doses of iodine (i.e. treats, housemates' diet, etc).

6. Radioactive iodine therapy (^{131} I) is considered the gold standard therapy in treating cats with hyperthyroidism due to its safety and efficacy. [11] Beta particles emitted from the radioiodine destroy functional thyroid tissue while sparing atrophic thyroid tissue and other important cervical structures. Success rates are up to > 95%. Hypothyroidism can be a consequence of radioiodine therapy however one publication studied the efficacy of treatment and incidence of hypothyroidism when administering lower dose radioiodine –2 mCi- compared to the standard treatment of 4 mCi. Results showed that those cats receiving the lower dose radioiodine had equivalent success rates of treating hyperthyroidism with a lower incidence of developing overt and subclinical hypothyroidism compared to the standard treatment group.[12]
7. Thyroidectomy: Surgical intervention may be an option in cats with hyperthyroidism. A technetium scan performed beforehand can be helpful in determining distribution of disease (bilateral vs unilateral) along with determining if ectopic tissue is present.
8. For hyperthyroidism-associated hypertension, amlodipine besylate has been the antihypertensive of choice given its proven efficacy. Initial starting dose of 0.625 mg PO per cat can be effective in lowering blood pressure however if systolic pressures are > 200 mmHg, the starting dose could be increased to 1.25 mg PO per cat.[13]
9. An angiotensin receptor blocker, telmisartan, has recently been FDA approved for the control of systemic hypertension in cats. ARBs are targeted RAAS blockers, and operate differently than amlodipine by selectively blocking the AT1 receptor and its vasoconstrictive function, among others. Although calcium channel blockers have been the recommended first-line treatment for hypertension in cats, recent studies report the success of telmisartan alone in controlling feline hypertension.[14-16]

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NOTES:

Chronic Enteropathy in Cats with Triaditis: Optimization of Diagnosis & Management

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Definition

The term "chronic enteropathy" refers to chronic disorders of the small and large intestine of unknown cause and are typically characterized by intermittent or continuous diarrhea, vomiting or weight loss of at least 3 weeks' duration. *Inflammatory bowel diseases (IBD)* and intestinal lymphoma comprise the 2 major chronic enteropathies of the cat. Both disorders are commonly associated with chronic vomiting, diarrhea, and weight loss in cats. Feline IBD is the term applied to a group of poorly understood intestinal disorders characterized by the infiltration of the gastrointestinal mucosa by inflammatory cells predominantly composed of variable populations of lymphocytes and plasma cells. Changes in the mucosal architecture characterized by villous atrophy, fusion, fibrosis, and lacteal dilation frequently accompany the cellular infiltrates. The cause of feline IBD is not well understood, but it is thought to be a consequence of uncontrolled intestinal inflammation in response to a combination of elusive environmental, enteric microbial, and immunoregulatory factors in genetically susceptible individuals. Knowledge of genetic susceptibility in cats with IBD is limited, with some studies reporting a predisposition for purebred cats such as Siamese.

Role of the intestinal microbiota in feline IBD

Dysbiosis of the intestinal microbiota has been demonstrated in cats with chronic gastrointestinal disease. Total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture and the density of cellular infiltrates, particularly macrophages and CD3+lymphocytes. The number of Enterobacteriaceae, *E. Coli*, and *Clostridium* spp. correlated with abnormalities in mucosal architecture (principally atrophy and fusion), upregulation of cytokine mRNA (particularly IL-1, -8 and -12), and the number of clinical signs exhibited by the affected cats, (Janeczo) underscoring the role of the density and composition of the intestinal microbiota on presence and severity of intestinal inflammation.

Gastrointestinal small cell lymphoma (T-cell phenotype) is the most commonly encountered form of lymphoma in cats, and is characterized by lymphoid infiltration of the stomach and/or intestines with or without mesenteric lymph node involvement. More recent articles have reported that up to 72% of the newly diagnosed feline lymphoma cases are alimentary in origin. Cats with GI lymphoma have a median age of 12 years and they are generally FeLV negative. Most cases of GI lymphoma involve the small intestine (particularly the jejunum), with a smaller percentage (approximately 18%) involving the stomach only. Approximately 8% of the GI lymphomas involve the large intestine only. There are 3 main histological types of gastrointestinal lymphoma in cats: diffuse small cell T-cell lymphoma, considered as a low grade lymphoma; large cell B-cell lymphoma, a high grade lymphoma which is considered more aggressive and usually involves the mesenteric lymph nodes; and large granular cell lymphoma which is the least common form of gastrointestinal lymphoma and carries an extremely poor prognosis. The concurrent diagnosis of lymphoplasmacytic IBD with small cell intestinal lymphoma has been well documented in cats, and the two disorders can occur concurrently. It has been postulated by multiple authors that the chronic inflammatory process precedes and acts as a trigger for the subsequent onset of gastrointestinal lymphoma. This was also reported by Moore et al, where 60% of the cats with lymphoma had prior clinical signs indicative of IBD.

Diagnosis of chronic enteropathy in cats

The diagnosis of chronic enteropathy is based on the presence of compatible clinical signs (chronic diarrhea, vomiting, weight loss, with or without borborygmus and flatulence), and the exclusion of metabolic, infectious, neoplastic, and obstructive disorders of the GI tract.

Physical examination findings reflect normal to thickened intestines, mesenteric lymphadenopathy, and loss of muscle mass. Abdominal effusion (ascites) and edema secondary to hypoproteinemia is extremely rare in cats with chronic enteropathy.

Diagnostic tests and procedures: The chemistry panel may reveal elevation in serum ALT secondary to a reactive hepatopathy (intestinal barrier dysfunction) or hepatobiliary disease and pancreatitis (triaditis). The CBC is typically unremarkable, apart from the anemia of chronic inflammation, however, peripheral eosinophilia can be documented in association with eosinophilic IBD, intestinal parasites, food intolerance/allergy, and mast cell disease. Measurement of serum cobalamin should be performed in all cats with chronic enteropathy given that cobalamin deficiency can produce similar signs to those associated with IBD, and response to IBD therapy will be suboptimal unless cobalamin concentrations are replete. Measurement of serum TLI is also important in cats with chronic weight loss and anorexia, given that 40% of cats with EPI are hyporexic or anorexic. Ultrasonographic findings in cats with

IBD and small cell lymphoma are similar (muscularis hypertrophy with or without concurrent thickening of the submucosal layer, and mesenteric lymphadenopathy); however, a normal ultrasound evaluation does not rule out intestinal lymphoma. In addition, mesenteric lymph nodes of most cats with IBD are more prominent and reactive on cytologic assessment, however, the presence of large, hypoechoic mesenteric lymph nodes is more suggestive of lymphoma, and the node(s) should be aspirated with ultrasound guidance to help confirm a diagnosis of lymphoma. Ultrasound is also a valuable diagnostic tool for assessing the pancreas, liver and spleen for evidence of disease.

Full-thickness vs. partial thickness biopsies
Gastrointestinal biopsies must show histological evidence of a moderate to marked infiltration of the gastrointestinal mucosa by inflammatory cells (predominantly lymphocytes and plasma cells) and changes in mucosal architecture for a diagnosis of IBD to be rendered. Previous studies have shown endoscopy with partial-thickness biopsies to be inferior to laparotomy with full-thickness biopsies for the diagnosis of lymphoma; however, many of the previous studies had significant limitations in their design and implementation and the findings must be interpreted cautiously. In the author's opinion, *the main limitation of endoscopic biopsies is the working length of the endoscope and not the inability to collect full-thickness biopsies.* The working length limitation appears to be is of lesser concern in cats because most of the jejunum can be accessed endoscopically during an esophagogastroduodenoscopy (EGD) procedure using an endoscope of appropriate length (140 cm). In addition, veterinary pathologists have relied on the presence of transmural invasion by cytologically atypical lymphocytes, in order to make a confident diagnosis of intestinal lymphoma. However, lymphoma manifests in the intestinal mucosa long before transmural progression, which may not even occur during the full duration of the disease process. Furthermore, an understanding of the mucosal immuno-architecture and lymphocyte trafficking patterns facilitates interpretation of transmural and endoscopic intestinal biopsy specimens. It is important to always perform ileal biopsies during colonoscopy, particularly in cats that are hypocobalaminemic. In addition, segmental involvement of the bowel with IBD or lymphoma has been well documented in the cat.

Molecular Clonality Assessment In Lymphoproliferative Disease
Immunohistochemistry and clonality are becoming more established for confirming gastrointestinal lymphoma and helping to differentiate lymphoma from inflammatory bowel disease (IBD). Expansion of T cell populations occurs in diffuse mucosal-associated lymphoid tissue (MALT) in feline inflammatory bowel disease (IBD) and feline intestinal lymphoma. The distinction of IBD and T-cell lymphoma, by morphological criteria alone, can pose difficulties, especially when mucosal infiltrates are more purely lymphocytic and lack the cellular heterogeneity often present in lymphoplasmacytic IBD. Molecular assessment of the clonality status of T cell infiltrates in feline intestinal disease is a valuable adjunct to morphological assessment and can be performed on formalin-fixed paraffin-embedded biopsy samples. Molecular clonality assays should be conducted as adjuncts to clinical, morphological and immunophenotypic assessment, with immunophenotypic assessment taking precedence over molecular clonality results for the determination of lymphocyte lineage. Molecular clonality analyses have the potential to facilitate earlier detection particularly of emerging T cell lymphoma in an inflammatory background such as that presented by chronic IBD.

Other Diagnostic Tests for Diagnosing Lymphoma
Histology guided mass spectrometry (HGMS) is a technology that allows for the analysis of endogenous molecules directly in formalin-fixed paraffin embedded (FFPE) tissue sections with the assistance of histopathology annotation for the targeted analysis of cell subpopulations. Preliminary studies using this modality reveal that mass spectrometry may be a powerful tool for differentiating feline IBD from small cell intestinal lymphoma.

There is a commercially available blood test marketed by Veterinary Diagnostics Institute (VDI) for helping to differentiate IBD from intestinal lymphoma. *The test (VDI-TK) measures thymidine kinase (TK) type 1 activity, which is involved in the synthesis of DNA precursors.* Serum TK levels allegedly correlate with the proliferative activity of tumor disease. A positive TK test indicates neoplasia and is usually present with lymphoma or leukemia. A negative test result does not rule out tumor proliferation. Low levels may be found in tumors of small mass or low proliferation. Elevated TK levels have rarely been detected in normal healthy cats. A study reported by VDI involving 60 cats (31 healthy controls, 18 cats with lymphoma, and 12 cats with IBD) revealed a sensitivity of 78% for the biomarker and a specificity of 91%. This study has not been published in the peer-reviewed literature for scrutinization and results should be interpreted with caution. A separate study published by Taylor et al. in J Fel Med Surg in 2012 evaluated serum TK activity in clinical healthy and diseased cats and showed that cats with lymphoma had a higher serum TK activity compared to healthy cats and cats with inflammatory disease. However, the receiver-operator curve (ROC) did not support the performance characteristics of the study reported by the manufacturer. In fact, the published sensitivity and specificity of the TK test in the Taylor study was 40% and 94.2% (false-positive rate 5.8%), respectively, with an AUC of 0.66, only slightly better than flipping a coin and substantially more expensive! In a nutshell, markedly increased serum TK activity is almost certainly lymphoma; however, there are many cases where the results will be less clear, particularly in those smoldering small-cell lymphoma cases with minimal proliferation.

MANAGEMENT OF IBD and INTESTINAL LYMPHOMA

Dietary Management

The importance of dietary intervention in the management of patients with IBD cannot be overemphasized. Less emphasis has been placed on the use of elimination diets or protein hydrolysates in cats with intestinal lymphoma, although the same principles of dietary therapy for both IBD and lymphoma should be maintained. Elimination diets containing novel, single protein sources or protein hydrolysates (selection based upon diet history) are typically utilized in affected animals. Owners should be educated about the importance of strict dietary compliance during the trial period, and any treats, supplements, and flavored medications should be avoided. The theoretical basis for the use of protein hydrolysate diets is that a reduction in immunogenic epitopes being presented to the mucosal immune system whilst dysregulation is present will increase the potential for resolution. Thus the argument for the use of a hydrolysate diet is independent of whether a dietary specific immunological response is suspected to be present or not. The ability to induce an antibody mediated hypersensitivity response appears to be dependent upon the size and structure of the protein. The allergens in soybean protein, for example, are between 20 and 78 kilodaltons, suggesting that soybean proteins with a molecular weight below this threshold would be less likely to illicit an immune-mediated response. Hypoallergenic diets are particularly beneficial as elimination diets for the diagnosis and management of food hypersensitivity, when a patient appears to be allergic to multiple allergens or when a complicated dietary history makes it difficult to identify a “novel” protein.

Pharmacologic Management of IBD and Intestinal Lymphoma

Cobalamin supplementation

Hypocobalaminemia is common in cats with chronic enteropathy, and was documented in 78% of 41 cats with GI small cell lymphoma (Kiselow). Cobalamin testing and supplementation if deficient (< 350 ng/mL) is thus pivotal given that hypocobalamemia will adversely affect the completeness of response to medical management. Supplementation of cobalamin can be performed parenterally (subcutaneously) or orally, and the decision is typically based on owners level of comfort and convenience. Injectable cobalamin is typically supplemented at 250-µg per cat (0.25 mL) SQ once weekly for 6 consecutive weeks, before reducing the frequency to once every 2-3 weeks for the indefinite future. Orally administered cobalamin should be supplemented at 250-µg (1/4 of a 1mg tablet) PO once daily for 2 consecutive months, before tapering to 250-µg PO given once every other day (Ruaux, 2005).

Other water-soluble vitamins

Vitamin and trace-element deficiencies can occur in feline patients with IBD. Vitamin K deficiency leading to coagulopathy has been reported to occur in cats in association with IBD. In the cats reported, the coagulopathy responded to parenteral vitamin K administration.

Prednisolone

Prednisolone is the backbone of medical management for cats with moderate to severe IBD and intestinal lymphoma. Most cats with IBD are started on prednisolone at 5 mg q 12 hrs (for average size cat), with a gradual taper over the ensuing 10-12 weeks for IBD. Cats with intestinal lymphoma are typically maintained on an alternate day therapy of 5 mg q48 hours for the indefinite future. Parenteral corticosteroid therapy is reserved for vomiting patients that cannot be well controlled with antiemetics, fractious cats, or animals with evidence of severe malassimilation in which the orally administered drugs will not be properly absorbed. Most cats with small cell lymphoma are typically managed with a combination of prednisolone (same dose as for cats with IBD) and chlorambucil, however, there is increasing practice of the administration of prednisolone as a single-agent in cats that are less clinically affected by their lymphoma. More aggressive therapy can then be started at a later timepoint if prednisolone alone is insufficient to induce a clinical remission. This staggered approach has been reported in a small number of people with milder forms of low grade intestinal lymphoma and no additional therapy was required in the 10-12 months of observation. In this way, chlorambucil is saved for future use, sparing the bone marrow from cumulative toxicity. Additionally, chlorambucil has become costly and this may provide an option for more cost-constrained pet-owners. Corticosteroids are still combined with adjunctive interventions such as diet change as well as cobalamin supplementation.

Budesonide

Budesonide is an orally administered corticosteroid structurally related to 16-hydroxyprednisolone, has high topical anti-inflammatory activity and low systemic activity because of its high affinity to the steroid receptor and rapid hepatic conversion to metabolites with minimal or no steroid activity. The drug is dosed at 1 mg once daily for cats, with a progressive tapering over an 8-week course. Budesonide is commonly used in place of prednisone in cats with a relative contraindication for systemic absorption of corticosteroids (e.g., diabetes mellitus). To date, budesonide has been infrequently used in feline patients with intestinal small cell lymphoma and a report by Pope in 2015 in which 3 cats received budesonide did not describe separate outcome information. Further controlled studies

comparing budesonide to prednisolone are warranted to assess efficacy and adverse effects in cats with intestinal small cell lymphoma.

Chlorambucil

The alkylating agent chlorambucil is beneficial for managing refractory cases of IBD (the drug is given in combination with prednisolone) and intestinal small cell lymphoma. Chlorambucil may be administered at a lower more dose frequent dose (2mg PO q48-72hr) or alternatively as a higher less frequent pulse dose, 15-20mg/m^2 PO over 1-4d, administered every 2-3 weeks. Both protocols are equally effective and the decision to implement either protocol is based on convenience for the owner. As an alkylating agent, the most common potential side effects are gastrointestinal and myelosuppressive in nature. In most studies, these side effects have been reported to be mild and self-limiting. Pope et al. focused more closely on toxicity and found 33.9% of cats experienced an adverse event, but nearly three-quarters (72.7%) were considered mild at a grade I or II, and only 8% of the events required supportive care. A small percentage of cats receiving this drug can have clinically significant cytopenias with platelets and neutrophils being most commonly affected. For this reason, it is important to continue monitoring complete blood counts (CBCs) throughout treatment as the myelosuppressive effects may manifest over time as in 1 cat reported to have a grade IV thrombocytopenia after 10 months of prednisone and chlorambucil (Lingard et al., 2009). Most often, these effects can be ameliorated with dose reductions or discontinuation of the chlorambucil depending on toxicity severity. Rarely, chlorambucil has been associated with other adverse effects such as liver enzyme elevation, Fanconi's syndrome, and neurologic effects (myoclonus). This highlights the need for continued biochemical monitoring with sustained therapy.

When Should Chemotherapy be Discontinued?

There is no "gold standard" approach to the duration of chemotherapy or tapering of drugs when managing cats with feline small cell lymphoma, and the decision is often based on clinician preference. At the author's institution, the decision to begin tapering is based on whether a clinical remission has been obtained and the duration of this remission. If remission is sustained for at least 3-6 months, then gradual tapering of the prednisolone can take place. Tapering of both prednisolone and chlorambucil should not occur simultaneously, and it is preferable to adjust only 1 drug at a time in order to better understand the impact of this change.

Rescue Therapy

Rescue therapy for feline intestinal small cell lymphoma has included multiple oral as well as injectable chemotherapy agents. Cyclophosphamide is one of the protocols employed in which one study demonstrated a 100% response rate and conferred a survival advantage over those cats not having received rescue therapy in another report (Fondacaro JV, 1999). Two small cell lymphoma rescue dosing schedules have been proposed, with one describing the division of 200-250mg/m^2 on a Monday and Wednesday administered every other week and the other consists of 250mg/^{2} every 3 weeks. Lomustine (CCNU) is another agent reported to have efficacy as a rescue for feline small cell lymphoma with a 69% clinical remission rate and a progression free interval of 169 days (Dutelle et al., 2012). Another study found a disease free interval of 332 days in 5 cats receiving CCNU rescue therapy. Lomustine is dosed at 50 mg/m^2 PO q 4 weeks (dose interval depending on white cell counts and adverse effects).

Prognosis of Cats with Small Cell Intestinal Lymphoma

Though it may take months for clinical remission to occur, response rates for prednisolone and chlorambucil are favorable, with 51-96% of cats attaining a complete clinical remission and an 86-95% overall remission rate. Moreover, long-term control of small cell lymphoma has been achieved with remission durations of 480d-1078d, and median survival times of 447d-1317d (Fondacaro JV, 1999; Kiselow et al., 2008; Lingard et al., 2009; Pope et al., 2015). As cats are most often middle to older age at the time of diagnosis, they may go on to die of unrelated causes.

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New Insights in Hepatic Disease Associated with Triaditis

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"Triaditis" is the term used to describe concurrent inflammation of the pancreas, liver, and small intestines, and has been reported in 50–56% of cats diagnosed with pancreatitis and 32–50% of those with cholangitis/inflammatory liver disease. The relationship among the 3 disorders and the specific pathogenesis of disease is currently not well understood, however, several theories have been raised. The unique anatomy of the feline cranial abdomen is considered to be a predisposing factor to simultaneous disease within these three organs, with the pancreatic duct joining the common bile duct before it enters the duodenum. In addition, differential involvement of host inflammatory and immune responses and enteric bacteria appear to play an important role. The combination of cholangitis and pancreatitis without concurrent lesions of IBD appears extremely uncommon, and the severity of IBD lesions and the presence of pancreatitis play critical roles in the overt clinical disease of “triaditis.”

Feline Inflammatory Liver Disease (Cholangitis)
Inflammation centered on the hepatobiliary system is a common form of hepatic disease representing one of the 4 most common hepatopathies in cats. The other 3 most common hepatopathies include hepatic lipidosis, hepatic neoplasia, and reactive hepatopathy. Based on the histological classification proposed by the WSAVA Liver Standardization Group feline cholangitis complex has been separated into 3 histological groups: Acute neutrophilic (suppurative) cholangitis, chronic neutrophilic (increased plasma cells, lymphocytes ± macrophages) cholangitis, and lymphocytic cholangitis. The new proposed classification scheme also prefers the term *cholangitis* to cholangiohepatitis, as inflammatory disruption of the limiting plate to involve hepatic parenchyma is not always a feature, and when present, is an extension of a primary cholangitis.

Acute neutrophilic (Bacterial) Cholangitis is characterized by infiltration of large numbers of neutrophils into portal areas of the liver and into bile ducts. *Disruption of the periportal limiting plate of the bile duct* results in necrosis of hepatocytes adjacent to portal areas and infiltration of neutrophils into hepatic lobules. Neutrophilic cholangitis may begin as an ascending bacterial infection within the biliary tract. Organisms include *E. coli*, *Bacteroides*, *Actinomyces*, *Clostridia*, and alpha hemolytic *Streptococcus*. Congenital or acquired abnormalities of the biliary system, including anatomic abnormalities of the gall bladder or common bile duct and gall stones may predispose to cholangitis. Inspissation of bile which may cause partial or complete obstruction of the common bile duct, gall bladder, or intrahepatic bile ducts frequently accompany cholangitis and may require treatment before the cholangitis can be controlled or resolved. Cats with acute cholangitis tend to be younger (mean age 3.3 years) than cats with chronic cholangitis (mean age 9.0 years) or hepatic lipidosis (mean age 6.2 years), and often have evidence of fever, anorexia, vomiting, and lethargy. Laboratory changes typically seen with acute cholangitis include mild neutrophilia with or without a left shift, normal to slight increase in serum bilirubin and serum alkaline phosphatase (SAP), and a substantial increase in alanine aminotransferase (ALT). This profile tends to differentiate acute cholangitis from chronic cholangitis, hepatic lipidosis, and hepatic neoplasia. Laboratory changes typical of chronic cholangitis include substantial increases in serum bilirubin, SAP, and ALT. Other associated changes may include mild-nonregenerative anemia, hyperglobulinemia, lymphocytosis, and hyperglycemia. When all inflammatory liver diseases are compared to hepatic lipidosis, hepatic lipidosis cases tend to have higher total bilirubin concentrations, and higher ALT and SAP activity. The hallmarks of hepatic lipidosis include jaundice, 10-fold or greater increases in ALT and SAP, without a corresponding increase in gamma glutamly transferase (GGT). In other forms of liver disease in cats, increases in GGT tend to parallel increases in SAP.

Lymphocytic Cholangitis is felt to represent a later stage of neutrophilic cholangitis, or may represent a separate immune mediated disease entity. It is characterized by a moderate to marked infiltration of the portal areas by small lymphocytes ± biliary hyperplasia, portal or periductal fibrosis, or bridging fibrosis. Many cases of lymphocytic cholangitis remain subclinical, whereas concurrent inflammatory diseases such as pancreatitis, IBD, or both are more likely to precipitate clinical signs.

Diagnostic Procedures

Abdominal Ultrasound
Abdominal ultrasonography is often helpful in evaluation of extrahepatic disorders associated with cholangitis. Bile duct abnormalities include gall bladder and/or common bile duct distention, cholelithiasis, cholecystitis, and bile sludging. Thick inspissated bile or choleliths are thought to be the result of deconjugation of the normally soluble conjugated bilirubin from the action of bacterial enzymes or

inflammatory products present in the biliary tree. Choleliths in cats are primarily bilirubin pigment stones that contain various amounts of calcium and other precipitates. The normal gall bladder is anechoic and appears round in the transverse scan and pear-shaped in the longitudinal scan. It is important to remember that gallbladder filling occurs normally with fasting, therefore, caution must be exercised in interpreting gall bladder enlargement in an anorectic or fasting cat. The common bile duct can usually be seen as an anechoic, tortuous, tubular structure 2 to 4 mm in diameter with an echogenic wall. Distention of the gall bladder and common bile duct (i.e. greater than 5 mm in diameter) occurs as a result of cholecystitis, or biliary obstruction. The gall bladder wall may become thickened as a result of inflammation or edema. The thickened gall bladder wall has a layered or "double-walled" appearance. Bile sludge within the gall bladder or common bile duct occurs commonly with inflammatory biliary tract disease and appears echogenic.

Liver Cytology/Histopathology
Liver cytology or tissue biopsy is essential in differentiating inflammatory liver diseases from hepatic lipidosis and neoplasia. The use of fine needle aspirates eliminates the need for anesthesia and markedly reduces the chance of hemorrhage. The diagnostic utility of liver cytology is controversial, particularly in inflammatory hepatopathies. Several reports indicate that cytologic evaluation is highly efficient in identifying hepatic lipidosis and hepatic lymphoma, however, inflammatory liver diseases are more difficult to identify cytologically. Results of another retrospective study, however, indicate poor correlation between liver cytology and histopathology. Cytologically, hepatic lipidosis is characterized by clusters of hepatocytes in which the cytoplasm is distended with lipid-filled droplets. Malignant lymphoma cells readily exfoliate and can be diagnosed by cytologic evaluation. Cytologic diagnosis of inflammatory liver diseases is hampered by blood contamination which introduces variable numbers of blood leukocytes into the samples. Therefore, the cytologist is left to determine whether leukocytes are of blood origin or represent inflammatory lesions within the liver.

Ultrasound-guided biopsy has significant limitations (particularly the quality and size of the biopsy specimen), and laparoscopy-assisted biopsies and laparotomies are recommended to procure liver biopsies. Ultrasound-guided fine needle aspiration of the gall bladder can be performed to obtain bile for aerobic and anaerobic bacterial culture. Culture of bile is superior to culture of liver parenchyma for the isolation of bacteria.

Fluorescence in situ hybridization (FISH)
Evaluation of fluorescence in situ hybridization (FISH) for the detection of bacteria in feline inflammatory liver disease facilitates determination of the presence and distribution of bacteria within the liver of cats with inflammatory liver disease (ILD) using eubacterial fluorescence. Histopathological findings from 39 cats with ILD and 19 cats with histologically normal livers confirmed non-specific reactive hepatitis (n=12), neutrophilic cholangitis (n=12), lymphocytic cholangitis (n=7), cholestasis/obstruction n=3), lymphoma (n=3), and acute hepatitis (n=2). Bacteria were observed in 21/39 cats with ILD and 3/19 cats with normal livers ($p = 0.0054$). Bacteria were mainly restricted to the outer liver capsule and may represent contaminants. However, the prevalence of intrahepatic bacteria was higher in ILD (13/31) compared to livers of normal cats (1/17), and were more frequently localized to portal vessels, venous sinusoids and parenchyma. Concurrent non-hepatic disease, predominantly pancreatic and intestinal (8/10 cats biopsied), was present in all 13 cats with intrahepatic bacteria. Bacterial culture was positive (predominantly *E. coli* and *Enterococcus* spp) in 11/23 (48%) samples, and concurred with FISH in 15/23 cases. The presence of intrahepatic bacteria in 41% of cats with ILD suggests a role in etiopathogenesis, and the distribution of bacteria within the liver supports the possibility of colonization via either enteric translocation or hematogenous seeding.

Treatment
Nutritional support is of paramount importance in cats with cholangitis, and many cats undergo nasoesophageal or esophagostomy tube placement to facilitate enteral nutritional support. Appetite stimulants such as mirtazapine or capromorelin can be tried in cats that are inappetent, but are less effective in cats that have been anorectic for several weeks. Mirtazapine has a first pass hepatic extraction and undergoes hepatic biotransformation and glucuronidation, warranting a 30-40% reduction in dose when using this drug in animals with hepatic dysfunction. Likewise, the dose of capromorelin should be reduced by approximately 30% in cats with hepatic dysfunction. Diazepam, oxazepam, and cyproheptadine (1 case) have each been circumstantially linked with development of fulminant hepatic failure in cats. Caution should be heeded to avoid force feeding cats in an effort to prevent conditioned food aversions. Injectable vitamin K_1 (3 doses of 0.5-1.5 mg/kg q 12 hrs SC or IM) should be proactively administered in all jaundiced cats with hepatic disease prior to intravenous catheterization, placement of an E-tube, and prior to liver aspiration or biopsy. Vitamin B12 deficiency is common, presumably reflecting inappetence, underlying inflammatory bowel disease, or intestinal dysbiosis. Theoretically, inadequate B12 may provoke hepatic lipidosis development.

Surgical intervention has been recommended if discrete choleliths or complete biliary obstruction is identified. When complete extrahepatic bile duct obstruction is identified, surgical decompression and biliary-to-intestinal diversion

(i.e. cholecystoduodenostomy or cholecystojejunostomy) is recommended. Bacterial culture and sensitivity testing of bile or biopsy specimens, choleliths, or gall bladder specimens, should be used to select appropriate antimicrobial agents whenever possible.

Antibiotics chosen for treatment of neutrophilic cholangitis or mixed cholangitis should ideally be based on culture and sensitivity testing of bile or liver parenchyma. In addition, if empiric antibiotic therapy is implemented, the selected antibiotic should be excreted in the bile in active form and should be active against aerobic and anaerobic intestinal coliforms. Tetracycline, ampicillin, amoxicillin, erythromycin, chloramphenicol, and metronidazole are excreted in the bile in active form, however, several of these have significant adverse side effects. Erythromycin is not effective against gram-negative bacteria, tetracycline is hepatotoxic, and chloramphenicol may cause anorexia. As a result, appropriate antibiotic choices include a fluoroquinolone, penicillin and metronidazole, or a fluoroquinolone together with a potentiated penicillin/clindamycin. Treatment with antibiotics for 4-6 weeks and occasionally longer is recommended.

Immunomodulatory therapy
Cats with lymphocytic cholangitis and culture negative liver biopsies are typically managed with a combination of prednisolone (1-2 mg/kg/day) with or without concurrent chlorambucil (2mg per cat q2-3 days). Biochemical values should be monitored prior to each reduction in dosage. If the clinical and biochemical response is satisfactory, doses of prednisolone as low as 0.5 mg/kg q 48 hours may be sufficient for long term maintenance.

Ursodeoxycholic acid (Actigall)
Bile sludging is best managed by treating the primary cholangitis, treating any biliary tract infection, and by the use of choleretic agents to increase the flow of bile. Ursodeoxycholic acid (Actigall®) has anti-inflammatory, immunomodulatory, and antifibrotic properties as well and can increase fluidity of biliary secretions. Ursodeoxycholic acid has been safely administered to cats at a dose of 10 to 15 mg/kg q24h PO. Complete obstructions may require surgery and in rare conditions a cholecystoduodenostomy or cholecystojejunostomy is required.

Antioxidants (e.g., Denamarin which contains SAMe and Silybin)
Treatment with antioxidants such as denamarin should be administered in all cats with cholangitis. Hepatic encephalopathy appears to be relatively uncommon in cats with acquired liver diseases and is manifest most frequently by excessive salivation. Hepatic encephalopathy can be managed by giving lactulose orally (0.5-1.0 ml/kg q8h PO) with or without addition of enteric antibiotics (neomycin 20 mg/kg q8-12h PO or amoxicillin 22mg/kg q 12h).

Prognosis
Response of cats with cholangitis to therapy should be monitored through use of serial complete blood counts and chemistry profiles. Persistent increases in ALT activity and serum total bilirubin concentration and/or increasing SAP activity suggest that treatment has been inadequate. Limited studies of the response of cholangitis cases to antibiotic treatment have been published, however, most cats with neutrophilic cholangitis recover with appropriate treatment and recurrence is rare with reported survival times of several years. Concurrent disease may affect long-term outcome in some cats. The median survival time for cats with lymphocytic cholangitis ranges from 26-36 months with treatment.

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Lessons Learned: Diagnosis & Management of Exocrine Pancreatic Disorders in Cats with Triaditis

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Pancreatitis is a highly prevalent disease of cats that may be associated with severe clinical disease and high mortality. A study conducted by the author and colleagues assessed the prevalence of pancreatitis in a cohort of 115 cats presented for necropsy irrespective of the cause of death and documented an overall prevalence of pancreatitis in 67% of the cats (De Cock, et al. 2007). Histopathologic features of chronic pancreatitis were observed in 69 cats (60%) whereas acute pancreatitis was observed in 16% of the cats. There was a significant correlation between age and occurrence of chronic pancreatitis, and a significantly higher prevalence of chronic pancreatitis in the left limb of animals with GI disease. Caution should be heeded in the interpretation of these findings because the detailed examination of the entire pancreas detected very mild lesions that were likely of no clinical consequence. The finding is also supported by the observations of Steiner et al., who found a discrepancy between the prevalence of pancreatitis in clinical and pathologic studies from which they concluded that a significant number of cats have subclinical pancreatitis.

Co-morbidities of feline pancreatitis include hepatic lipidosis, inflammatory liver disease, bile duct obstruction, diabetes mellitus, inflammatory bowel disease, vitamin deficiency (B12/cobalamin, folate or K), intestinal lymphoma, nephritis, pulmonary thromboembolism and pleural and peritoneal effusions. "Triaditis" has been variably reported in 50-56% of cats diagnosed with pancreatitis.

Etiopathogenesis of pancreatitis

The etiopathogenesis of pancreatitis is incompletely understood and several theories have been proposed. A variety of potential triggers have been associated with the development of feline pancreatitis including enteric bacteria that have been observed in 35% of 31 cats with moderate to severe pancreatitis. Other infectious predisposing causes include *Bartonella*, *Toxoplasma gondii*, FIP, and virulent systemic calicivirus. Other triggers include immune mediated disease, trauma, organophosphate toxicity, acute hypercalcemia, and idiosyncratic drug reaction. Bacterial infection most likely arises via ascending colonization of the pancreatic duct or hematogenous seeding of translocated bacteria. Fluorescence in situ hybridization documented bacteria in the pancreas of 13/46 cats with pancreatitis, and colonization was more common in moderate to severe pancreatitis. The role of pancreatitis in triaditis is a hotly debated subject, with several plausible mechanisms in vogue: 1) Acute pancreatic inflammation could induce intestinal inflammation via direct contact with juxtaposed duodenum and colon, which promotes intestinal dybiosis and the translocation of enteric bacteria to the pancreas and liver across the inflamed leaky bowel or via the pancreatico-biliary duct. Pancreatitis and intestinal inflammation could precipitate a reactive hepatopathy or neutrophilic cholangitis via translocation of bacteria. This theory is plausible in light of the enteric bacteria spp. (*E. coli*, *Enterococcus* spp., *Bacteroides* spp., *Streptococcus* spp., *Clostridium* spp., and *Salmonella* spp.) in liver and bile of cats with cholangitis diagnosed via culture and fluorescence in situ hybridization (FISH) methodologies. 2) A second theory is associated with intestinal inflammation as the primary trigger that promotes dysbiosis and the translocation of enteric bacteria to the pancreas and liver across the inflamed intestines or pancreatico-biliary duct. The localization of bacteria in cats with inflammatory liver disease to portal vessels, venous sinusoids and parenchyma (in contrast to bile ducts) increases the likelihood of enteric translocation or hematogenous seeding as the more likely route for infection. 3) Lastly, a third consideration for the etiopathogensis of pancreatitis could involve an immune-mediated process against enteric bacteria.

Treatment

The management of cats with triaditis has been discussed in the proceedings focused on hepatic disease and chronic enteropathy, however, several additional considerations warrant discussion for the management of feline pancreatitis.

Nutritional support

There is no indication to fast the cat unless it is vomiting intractably and at increased risk for aspiration pneumonia. In addition, dietary fat does not appear to delay gastric emptying compared to the dog, and dietary fat restriction is not typically recommended for cats with pancreatitis. Nasogastric tube feeding was relatively well tolerated in 55 cats with suspected acute pancreatitis, and was associated with a low incidence of diarrhea, vomiting, and mechanical complications.

Intravenous fluid therapy

Crystalloids, colloids, plasma (for management of DIC)

Analgesia
Buprenorphine (0.005-0.01 mg/kg SQ q6-12 hrs); fentanyl (25 µg/hr patch q 5 days). Adequate fentanyl levels are not attained for between 6-48 hrs after application, so another analgesic should be administered in the short term. Maropitant reduces visceral pain and can also be implemented as a useful adjunct.

Antiemetics
Maropitant (1mg/kg IV (inject over 60-90 seconds) q 24hrs; ondansetron (0.5 mg/kg SQ, PO, or IV q12hrs); chlorpromazine (0.2-0.4 mg/kg SQ q 12hrs)

Antibiotics
Only considered with increased likelihood of bacterial translocation (sepsis, fever, neutrophilia with a left shift on CBC, clinical signs of sepsis). Bacterial spp. are similar to those associated with inflammatory liver disease and the same recommendations for management of acute cholangitis are made (amoxicillin plus clavulanic acid, metronidazole, and/or fluoroquinolone).

Acid Suppressants
Acid suppressants such as famotidine and omeprazole should not be routinely implemented unless there is evidence of breakdown of the intestinal mucosal barrier or evidence of a gastric or intestinal ulceration. The acid suppressants can also be implemented to help prevent reflux-associated esophagitis in cats with intractable vomiting. The proton pump inhibitors (PPIs) are more potent than the H2-receptor antagonists, and are not susceptible to tachyphylaxis, a phenomenon that has been documented in cats and is associated with a progressive reduction in effectiveness of H2-receptor antagonists such as famotidine after 3 days of continuous administration. Proton pump inhibitors such as omeprazole should always be administered twice daily approximately 30-45 minutes before meals. Lastly, PPIs should always be tapered if administered for > 10 days to prevent massive acid rebound hypersecretion.

Exocrine Pancreatic Insufficiency
Exocrine pancreatic insufficiency (EPI) is characterized by inadequate production of pancreatic enzymes from pancreatic acinar cells and has been diagnosed with increasing frequency with the advent of the feline trypsin-like immunoreactivity (fTLI) assay. The most common cause of EPI in cats is secondary to chronic pancreatitis, and there are important differences in the clinical presentation of cats vs. dogs with EPI. The median age of cats with EPI was 7.7 years in a large retrospective case series involving 150 cats; however, the age range was extremely wide ranging from 3 months to almost 19 years. This is important because EPI has been traditionally considered to be a disease of middle-aged to older cats. Potential causes of EPI in younger cats could include pancreatic acinar atrophy, pancreatic hypoplasia or aplasia, and *Eurytrema procyonis* infestation. The most common clinical sign was weight loss (> 90%); however, hyporexia was documented in 40% of cats and diarrhea was present in only 62% of cats which is much lower than that reported in dogs with EPI. Importantly, the clinical presentation of many cats with EPI did not closely resemble the typical presentation seen in dogs. Thus EPI should be considered in any feline patient with unexplained weight loss or anorexia even when clinical signs of diarrhea and polyphagia are not present. Serum cobalamin concentration was frequently decreased (77%) warranting supplementation. Overall, response to treatment was considered good in 60% of affected cats, which is similar to that reported in the dog.

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How Chronic Disease Affects Pain Perception & Management

Elizabeth Colleran, DVM, MS, DABVP (Feline)

Frailty

In human medicine, there is accumulating evidence that frailty is becoming one of the world's most serious health issues.[i] Given the longevity that companion cats are experiencing, at least in North America, it could be reasoned that an understanding of frailty and its constituent parts would be useful toward an understanding of the differences that occur in cats as they experience the many physical manifestations of disease. This understanding will provide a platform toward a clearer picture of planning interventions and management strategies for cats with comorbidities.

Frailty is a geriatric condition characterized by an increased vulnerability to external stressors. It is strongly linked to adverse outcomes. Frailty is different from aging, disability and co-morbidity although it is distinctly related to these factors. For example, although frailty prevalence increases with age, it occurs independently of chronological age.

Frailty does not yet have an internationally recognized standard definition, although the general premise is that frailty may be considered to be a geriatric syndrome reflecting multi-system dysfunction and in which individuals are able to dynamically transition between severity states. Multiple reasons exist as to why it is so difficult to define frailty, including: its complex etiology, the often independent work of frailty researchers and the inherent difficulty in distinguishing frailty from both aging and disability.

Frailty has a strong biological component and it is thought to result from cumulative cellular damage over the lifetime. The specific pathophysiological pathways underpinning frailty are not yet clearly known al though there is evidence that both malnutrition and sarcopenia may have similar causal pathways. Inflammation is one such pathway and is well-established as a causal factor in frailty. Pro-inflammatory cytokines can influence frailty either directly, for example by promoting protein degradation or indirectly by altering metabolic processes.[ii]

The biological causative mechanisms of frailty are different than those causing aging. Frailty occurs when not one, but multiple physiological processes decline. The more systems that are in a diminished state, the greater the likelihood of frailty. While physiological systems do lose some of their homeostatic reserve at advanced ages, there is an inherent reserve or buffer, suggested in humans to be about 30% which an individual can lose ands still function well. Frailty is thought result when this threshold is surpassed in multiple physiological systems – so much so that repair mechanisms cannot maintain system homeostasis. Pre-frailty (latent) frailty is thought to be the silent precursor to frailty, manifesting as frailty when external stressors, such as acute illness, injury or psychological stress occur. [iii]

All of this has yet to be studied, described or quantified in cats, despite the importance of separating illness and degenerative conditions from frailty and chronological age. Aging refers to the natural and progressive series of life stages. Although it is often misunderstood to be a pathologic process, it is the normal time dependent changes that occur in the life of every organism. Disease must be distinguished from aging as conditions for which interventions are possible and desirable. Frailty must be distinguished from disease, chronological aging and disability in order to plan interventions that address the loss of reserves that define it.

Pain

Chronic pain should not be considered a symptom but a disease in its own right since it may be present in the absence of a primary cause, has many consequences in the affected organism that can alter system functions of all varieties. Nociceptive signaling alters the spinal cord and higher centers creating the potential for developing pain signals from the central nervous system (CNS) itself. The end result of these CNS changes is spontaneous pain, hyperalgesia (increased response to painful stimuli by expansion, protraction or exaggeration) and allodynia (pain from normally nonpainful stimuli)

Multiple conditions may be present that each contribute to the pain experienced over time. Inflammatory is associated with tissue injury and direct stimulation and sensitization of nociceptors following activation of the inflammatory cascade. Neuropathic pain is caused by a lesion or disease of the somatosensory system both peripherally and centrally. Functional pain is not associated with any detectable inflammatory or neuropathic etiology.[iv] All of these can be present in a single patient and result in persistent pain, difficult to isolate and treat.

Inflammatory	*Neuropathic*
Degenerative joint disease	***Nerve compression***
Cancer	***Cancer infiltration***
Dental and oral disease	***Amputation***
Ocular conditions/injuries	***Nerve resection***
Gastritis	***Intervertebral disc disease***
Inflammatory bowel disease	***Trauma***
Interstitial cystitis	***Chemotherapy***
Constipation	***Diabetic neuropathy***
Trauma	
Radiation/chemotherapy	
Chronic kidney disease	

Age associated behavioral changes can overlap with behavior changes related to chronic pain and every effort must be made to distinguish the two. Chronic pain must be ruled out before assuming that behavioral changes are age-related only. These behavioral changes are different than those manifested by humans or dogs with chronic pain; pain may go undetected by caregivers. A "pain trial" may be a valuable tool when pain is suspected but uncertain. Analgesics can be administered or prescribed; a decrease or resolution of clinical signs often confirms the diagnosis of chronic pain.

The most commonly cited source of chronic pain is degenerative joint disease. Occurring commonly in cats over the age of nine implies that it will be present with other potentially painful conditions. This constellation of pain and the effects it has both physiologically and emotionally cannot be overstated. Plasticity of the nociceptive transmission system results in increased sensitivity, hyperalgesia and allodynia.

In the veterinary setting, assessing a cat's emotional and physical characteristics is often confounded by the stress of taking this territorial animal out of his home range and surrounding him with strangers. It can be especially challenging to assess gait and chronic musculoskeletal pain in an animal whose instinct is to freeze or flee. With this in mind, a validated pain score has been developed the Feline Musculoskeletal Pain Index (FMPI) which gives the power of observation to caregivers in the home. Questions are addressed towards specific indicators using accessible language. [v]

Other causes of pain included cancer pain which is caused by several mechanism, some or all within the individual patient. Inflammatory pain is caused by tumor growth and destruction of adjacent tissues and structures. Visceral pain can be caused by distension; neuropathic pain by nerve compression or a primary tumor of the nervous system. Cancer treatment including surgery, chemotherapy and radiation therapy are common causes of pain. Periodontal disease is another common comorbidity particularly in older cats. If there is inflammation in the oral cavity there is pain present. Dysphagia, pawing at the mouth during or after eating and other less obvious signs – food preference changes, eating behavior, avoidance and reluctance to be petted around the head – are all indicators that pain is present. [vi]

Any chronic condition affecting the gastrointestinal system and causing visceral distension such as megacolon or constipation is painful. Inflammatory bowel disease is chronic intestinal inflammation often occur concomitantly with pancreatitis or cholangitis. These inflammatory conditions should all be considered chronic abdominal pain sources.

Treatment

Appropriate assessment of chronic pain is critical to successful treatment in the cat with one or more comorbidities. Identification of a primary cause will facilitate treatment only if all of the other potential sources of pain have been included in the assessment. The relationship of the owner to the cat must remain a paramount consideration when planning therapy. Preservation of the powerful bond between a caregiver and beloved cat is crucial to the well-being of everyone involved. Understanding the pathophysiology of the painful condition is required to make a plan for long term therapy.

A questionnaire like FMPI or one that is arrived at in consultation with the owner that assesses behavior changes can be repeated over time to assess whether or not the pain management modalities chosen for the patient are working. Each "score" is compared to previous ones to visualize trends, identify patterns of behavior and improve outcomes. This information is used to make adjustments, or provide evidence that the plan is improving the life of the patient. Pain management plans tend to have several components, including pharmaceuticals (e.g. NSAIDs, analgesics), nonpharmaceutical anti-inflammatory devices (e.g. laser therapy, Assisi Loop) and nonpharmaceutical additions (e.g. heat, furniture adjustment, ramps), so a reliable, verifiable and validated survey for judging which combination of multimodal pain management is best for this patient is required. v

Challenges in the treatment of chronic pain in cats:

- Difficulty recognizing and assessing resulting in ineffective treatment
- Fear of adverse effects
- Lack of cat-specific data on pharmaco-kinetics and –dynamics
- Individual variability in response
- Failing to implement multi-modal approach
- Cost
- Caregiver compliance, time commitment and expectations[vii]

Case examples will be discussed.

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What Makes a GI Pathogen, Pathogenic?

Michael Lappin, DVM, PhD, DACVIM

Clinical problem and differentials

Vomiting is the forceful ejection of stomach and proximal duodenal contents through the mouth. Vomiting can be induced by vestibular, vagal, chemoreceptor trigger zone, or direct input to the emetic center. Diarrhea is a characterized by increased frequency of defecation, increased fluid content of the stool, or increased volume of stool. Markedly increased frequency of defecation, small volume stools, tenesmus, urgency, hematochezia, and mucus are consistent with large bowel diarrhea. Slight increase in frequency of defecation, large volume, melena, steatorrhea, and polysystemic clinical signs are more consistent with small bowel diarrhea. Mixed bowel diarrhea is a combination of characteristics or clinical signs.

Gastrointestinal (GI) signs can be the result of primary diseases of the GI system or secondary GI diseases. The secondary GI diseases are generally those of the kidneys, liver, pancreas (pancreatitis or exocrine pancreatic insufficiency), endocrine system (hypoadrenocorticism; diabetic ketoacidosis; hyperthyroidism), or central nervous system. Differential diagnoses for primary GI diseases are often grouped into obstruction (masses, foreign body, and intussusception), dietary intolerance, drugs/toxins (garbage gut), inflammatory gastric and bowel diseases, neoplasia, infectious diseases, and parasites.

The primary bacteria associated with gastrointestinal tract disease in cats include *Salmonella* spp., *Campylobacter jejuni*, *Clostridium perfringens*, *Helicobacter* spp., bacterial overgrowth syndrome, bacterial peritonitis, and bacterial cholangiohepatitis.[1-3] The primary viral agents include feline coronaviruses, feline leukemia virus, feline immunodeficiency virus, and feline panleukopenia virus.[4-6] The primary nematodes are *Ancylostoma*/*Uncinaria, Strongyloides cati*, *Dirofilaria immitis* (vomiting), *Toxocara cati*, *Toxascaris leonina*, *Ollulanus tricuspis*, and *Physaloptera* spp. Enteric protozoans include *Giardia* spp., *Cystoisospora* spp., *Cryptosporidium* spp., *Entamoeba histolytica*, and *Tritrichomonas foetus (blagburi)*.[7-18] The cestodes *Taenia*, *Dipylidium*, and *Echinococcus* generally cause subclinical infection.

Diagnostic procedures

In cats with suspected infectious or parasitic causes of gastrointestinal signs, I perform a centrifugation procedure to evaluate for eggs, cysts, and oocysts of GI parasites. If small bowel diarrhea is occurring, the addition of a *Giardia* antigen assay to the fecal flotation increases the *Giardia* spp. sensitivity to around 97%. In cats with small bowel diarrhea, acid-fast staining of a fecal smear or immunofluorescence antibody staining (Merifluor *Giardia/Cryptosporidium*, Meridian Diagnostics) can be used to find *Cryptosporidium felis* oocysts. A wet mount examination may aid in identifying the motile trophozoites of *Tritrichomonas* (large bowel diarrhea) and *Giardia* (small bowel diarrhea). If neutrophils are evident on rectal cytology and particularly if fever is also present, I recommend fecal culture for *Salmonella* spp. and *Campylobacter* spp.. PCR assays can also be used to amplify the DNA of *Salmonella* spp. and *Campylobacter* spp., but do not provide antibiotic susceptibility. If spore-forming rods consistent with *Clostridium perfringens* are present in large numbers, fecal enterotoxin assays or PCR assays can be performed to help confirm the diagnosis. However, these assays can be positive in healthy cats as well and so have less than 100% predictive value. If infectious diseases are on the primary differential list, other PCR assays can be considered. While the *Giardia* PCR assay is less sensitive that the combination of fecal flotation and Giardia antigen test, the *Cryptosporidium* PCR assay is more sensitive than FA. If I perform *Giardia* PCR assays, it is generally to determine whether the cat harbors a zoonotic assemblage (www.dlab@colostate.edu). Coronavirus RT-PCR assay results do not correlate with the potential to develop feline infectious peritonitis nor the presence of diarrhea. Occasionally, parvovirus PCR assay results will be positive in cases with panleukopenia even when antigen tests are negative. However, parvovirus PCR assays also amplify the DNA of panleukopenia vaccines. Cats with large bowel diarrhea without evidence of *T. foetus* trophozoites on wet mount examination should be evaluated by PCR assay.

What makes a pathogen?

Each of the agents discussed so far can be detected in cats with and without gastrointestinal signs of disease. Thus, as discussed, positive test results do not guarantee a response to therapy. Clinically, it can be difficult to determine why a pathogen like *Giardia* spp. can be an apparent cause of diarrhea in one cat and be carried by other cats that have normal stool character. In some cases, the strain of the pathogen may be more virulent than others. In other cases, there may be an underlying pathology that has not been detected like inflammatory bowel disease. It is also possible that in individual cats, presence of co-infections may potentiate disease manifestations. Underlying immune deficiencies may be occurring. In most cases with clinical signs of gastrointestinal disease, the fecal microbiome is abnormal. In the lecture, clinical examples of each of these possibilities will be presented.

Infectious disease treatment options

Since it can be difficult to determine whether a disease agent is associated with clinical signs, non-specific treatments are often tried. Cats with GI signs of disease are usually fed a diet that is formulated for benefit the type of diarrhea (large or small bowel). Each year there are new papers supporting the use of probiotics in the management of gastrointestinal diseases and so many clinicians prescribe probiotics to aid in the management of GI diseases. Cats with clinical signs of disease that are shown to harbor infectious or parasitic agents usually have specific treatments prescribed.

There are multiple drugs used in the treatment of gastrointestinal parasitic infections. For all kittens, the strategic deworming recommendations for the control of hookworm and roundworm infections from the Companion Animal Parasite Council (www.capcvet.org) or the European Scientific Counsel Companion Animal Parasites (www.www.esccap.org/guidelines/) should be followed by veterinary practitioners. In endemic areas, monthly *D. immitis* preventatives can help control or eliminate some nematode infections as well as prevent heartworm infection. *Dipylidium* and *T. taeniaformis* infestations usually are eliminated by praziquantel or espiprantel; fenbendazole is effective for *T. taeniaformis*. Since *Echinococcus multilocularis* can be a significant zoonosis transmitted to cats by carnivorism, hunting cats in endemic areas should be treated up to monthly. Administration of a pyrantel/praziquantel combination may be effective in these cats since praziquantel is approved for the treatment of *Echinococcus* and roundworms are also transmitted by carnivorism.

Withholding food for 24 to 48 hours is indicated in cats with acute vomiting or diarrhea. Highly digestible, bland diets are used most frequently if vomiting and small bowel diarrhea are the primary manifestations of disease. High fiber diets are generally indicated if large bowel diarrhea is occurring. Diarrhea associated with *Giardia* spp. generally resolves during or after administration of fenbendazole or metronidazole. In one study, cyst shedding resolved in 26 cats after the administration of metronidazole benzoate at 25 mg/kg, PO, q12hr for 7 days. If inflammatory changes exist, metronidazole may also be beneficial due to inhibition of lymphocyte function. Central nervous system toxicity occasionally occurs with this drug; it is unlikely if no more than 50 mg/kg, PO, total daily dose is given. However, since microbiome changes are also induced by metronidazole, some clinicians now recommend use of fenbendazole first for the treatment of feline giardiasis.

Fenbendazole has not been studied extensively for treatment of giardiasis in cats. In one experiment study of cats coinfected with *Giardia* spp. and *Cryptosporidium* spp., four of eight cats treated with fenbendazole at 50 mg/kg, PO, daily for 5 days stopped shedding *Giardia* cysts.[8] The combination product of febantel, pyrantel, and praziquantel has been shown to have anti-Giardia activity in dogs. When given at the febantel dose of approximately 56 mg/kg, PO, daily for 5 days, *Giardia* cyst shedding was eliminated in some cats.[9] Metronidazole and fenbendazole can be given concurrently in resistant cases. A single dose of secnidazole was evaluated in one trial and is being used with groups of cats need to be treated in the United States.[10] Ronidazole and tinidazole also have anti-*Giardia* activity in cats, but I reserve the use of these drugs for the management of *T. foetus* infections.

In some cats with *Giardia* and diarrhea, administration of a probiotics or addition of fiber to the food and retreating can result in resolution of diarrhea. In one study in our laboratory, use of *Enterococcus faecium* SF68 with metronidazole was superior to metronidazole alone in a study of shelter dogs with diarrhea (Nestle Purina; FortiFlora). The primary goal of *Giardia* therapy is to resolve diarrhea. It is unlikely the infection can be eliminated in most cats and reinfection is common. If treatment is to be monitored, a fecal flotation (not antigen assay) should be performed within 48 hours of stopping therapy (www.capcvet.org).

Multiple drugs have been evaluated for the treatment of cats with *T. foetus* infections; until recently no drug eliminated infection and diarrhea rarely resolves during the treatment period. Ronidazole at 30 mg/kg, PO, q24hr, for 14 days eliminates clinical signs of disease and trophozoites from many affected kittens. Ronidazole is more neurotoxic than metronidazole and so should be used carefully. In another one small study, administration of metronidazole and enrofloxacin lessened diarrhea in kittens but it is unknown if the organisms infecting those cats was *T. foetus*. It is possible that some cats with *T. foetus* have other enteric coinfections and so antihelmintics or drugs with activity against *Giardia* spp., *Cryptosporidium* spp., and enteric bacteria like *Campylobacter* spp. are often prescribed. Paromomycin should be avoided cats with bloody stools because of the potential for being absorbed and inducing renal disease or deafness. Quinolones, especially pradofloxacin, may be an alternate therapy for cases resistant to ronidazole.

Cryptosporidium spp. associated diarrhea sometimes resolves after administration of tylosin (10-15 mg/kg, PO, BID for at least 14 days) or azithromycin (10 mg/kg, PO, daily for at least 14 days). If the cat is responding to therapy, continue treatment for 1 week past clinical resolution. Some cats may require several weeks of treatment. Nitazoxanide at 75 mg/kg, PO, twice, 14 days apart may have some effect against *C. canis* in dogs but data in cats using this protocol is lacking.

The *Toxoplasma gondii* oocyst shedding period can be shortened by administration of clindamycin, sulfadimethoxine, or ponazuril. *Cystoisospora* spp. should be treated with ponazuril or toltrazuril.[20, 21]

Since many of the gastrointestinal parasites that infect cats are transmitted by carnivorism, cats should not be allowed to hunt or be fed raw meats. Additionally, infection of cats by many feline parasites results from ingestion of contaminated water. Clinical disease in some parasitized cats can be lessened by eliminating stress and providing a quality diet and clean environment.

Clostridium perfringens and bacterial overgrowth generally respond to feeding an appropriate diet and use of probiotics. *Enterococcus faecium* strain SF68 (FortiFlora® Purina Pet Care) was used to lessen non-specific diarrhea in cats in a shelter from over 20% to < 5%.[22] Some *C. perfringens* cases will also require an antibiotic; tylosin, metronidazole, ampicillin, amoxicillin, or tetracyclines. The diarrhea associated with cases with suspected clinical salmonellosis or campybacteriosis should be managed with an appropriate diet and a probiotic rather than oral antibiotics due to the potential for selection of resistant strains. Parenteral antibiotics can be used if signs of bacteremia exist. Appropriate antibiotics for the empirical treatment of salmonellosis while awaiting susceptibility testing results include chloramphenicol, trimethoprim-sulfa, amoxicillin; quinolones are also effective. *Helicobacter* spp. infections are usually treated with the combination of metronidazole and tetracycline or amoxicillin and metronidazole in dogs. Clarithromycin or azithromycin may be logical choices in cats since the species is often difficult to treat with multiple drugs. Whether to concurrently administer an antacid like famotidine is controversial but seems to lessen vomiting in some cats.

Cats with apparent bacteremia due to enteric bacteria should be treated with parenteral antibiotics with a spectrum against anaerobic and gram negative organisms. The combination of enrofloxacin with a penicillin or first generation cephalosporin is generally effective. Second generation cephalosporins or imipenem are also appropriate choices.

Panleukopenia virus, feline leukemia virus, feline immunodeficiency virus, and coronaviruses are the most common viral causes of gastrointestinal tract disease in cats. Viral diseases are managed by supportive treatment. Make sure to maintain hydration, correct hypoglycemia, and maintain normal potassium concentrations. Use of jugular catheters is superior to leg veins since blood samples can be drawn and CVP can be measured. Based on results in dogs with parvovirus infection, administration of plasma or serum (1 ml/kg) from a hyperimmune blood donor cat may lessen morbidity in cats with panleukopenia due to passive transfer of immunity. This is effective because parvoviruses induce a viremic state; virus particles are complexed by the antibodies transferred passively. Administration of interferon alpha 2b (USA; compounding pharmacies) or feline interferon (Europe; Virbac) may beneficial. Parenteral administration of antibiotics effective against gram negative and anaerobic bacteria are commonly used if signs of sepsis are apparent.

Histoplasma capsulatum infection is the most common fungal infection of the gastrointestinal tract of cats in the United States. Treatment with itraconazole can be effective.

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NOTES:

The Role of Coinfections in Select Feline Clinical Disease Syndromes

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Introduction

With the proliferation of the use of polymerase chain reaction assays and other assays combined in panels, there is increasing evidence that cats are commonly infected with more than one organism that may be considered pathogenic.

The presence of co-infections can potentiate illness in some situations. In addition, when multiple infections are present, it can be difficult for the clinician to ascertain which agent is the most important cause of the clinical manifestations.

Please see the sections of the proceedings of this meeting for discussions of co-infections in retrovirus infected cats, cats with gastrointestinal signs of disease, and with chronic upper respiratory tract infections.

At the meeting, cases will be used to emphasize some of the more commonly recognized coinfections that may play a role in acute upper respiratory disease, mucositis, and fever associated with blood borne infections like *Anaplasma phagocytophilum*, *Bartonella* spp., *Borrelia burgdorferi*, *Ehrlichia* spp., and the hemoplasmas. The following notes are to be used as supplements for the blood borne agent discussions. Coinfections with flea borne and tick borne agents may be common.[1]

Anaplasmosis

Cats have shown to be susceptible to *A. phagocytophilum* infection after experimental inoculation. DNA of *A. phagocytophilum* has been amplified from naturally exposed cats in multiple countries including Sweden, Denmark, Ireland, Poland, and the United States.[2-5] Any region known to be endemic for *Borrelia burgdorferi* infection in dogs is endemic for *A. phagocytophilum*. Cats living in endemic areas are commonly seropositive but most do not have clinical signs of disease. As in dogs, *A. phagocytophilum* is transmitted by *Ixodes* ticks and so infections of cats are likely to be most common in these areas.

While the pathogenesis of disease associated with *A. phagocytophilum* in cats is unknown, some cats experimentally inoculated with *A. phagocytophilum* developed anti-nuclear antibodies and increased IFN-gamma mRNA suggesting that an immune pathogenesis of disease may contribute to the clinical findings. Fever, anorexia, and lethargy are the most common clinical abnormalities in naturally infected cats. However, in a recent experimental study in my laboratory, cats infected with *A. phagocytophilum* by exposure to wild caught *Ixodes* spp. ticks remained clinically normal over the 70 day study period in spite of being PCR positive for *A. phagocytophilum* DNA in blood for several weeks.[4] Whether or not this agent is associated with chronic recurrent fever or other clinical abnormalities in cats is unknown. Many cats have evidence of co-infection by B. burgdorferi since both agents share the same vector.

Cats with fever in endemic areas can have blood smears examined cytologically but morulae are less commonly detected than in dogs. Some commercial laboratories offer serologic testing or PCR assays to amplify *A. phagocytophilum* DNA from blood. One commercial assay for detection of *A. phagocytophilum* antibodies in dog serum (SNAP 4DXPlus, IDEXX Laboratories) has been shown to detected these antibodies in feline sera.[4] Approximately 30% of cats with proven clinical infections induced by *A. phagocytophilum* are seronegative when first assessed serologically, but most of the proven cases evaluated to date have ultimately seroconverted. Some mountain lions with *A. phagocytophilum* DNA amplified from blood have been serum antibody negative and so a single negative antibody result in an acutely infected cat does not exclude infection. Therefore, cats with suspected anaplasmosis may need convalescent serum samples to prove infection. Alternately, antibody testing could be combined with PCR testing of whole blood in acute cases. Morulae can be identified in the neutrophils of some cats. Many cats will be antibody positive but not clinically ill.

Several antibiotics have been administered to naturally infected cats, but all cats in 2 studies became clinically normal within 24 to 48 hours after initiation of tetracycline or doxycycline administration and recurrence was not reported.[2,3,5] While clinically normal, 2 cats were still PCR positive 17 days and 90 days after treatment (of 21 to 30 days duration) which suggests that treatment with tetracyclines for 21 to 30 days may be inadequate for eliminating the organism from the body.[3] In a recent experimental study, bacteremia as determined by PCR assay was limited over several weeks.[4]

In regions with *Rhipicephalus sanguineus*, *A. platys* may also be detected and could be present as a co-infection with *E. canis*.[1, 6]

Bartonellosis

A number of *Bartonella* spp. including *B. henselae*, *B. clarridgeiae*, *B. koehlerae*, *B. quintana* and *B. bovis* have been cultured or amplified from client-owned cats with fever. Fever following experimental inoculation with *B. henselae* has been documented in a number of studies including a recent study in our laboratory where the CSU-1 strain of *B. henselae* induced significant fever in three of six cats after exposure to infected *C. felis*.[7] None of the six cats administered imidacloprid-moxidectin in that study became infected or febrile. However, not all strains or *Bartonella* spp. induce fever in all cats; for example in the imidacloprid-moxidectin study, cats inoculated with the same strain intravenously failed to develop fever. Whether fever will occur during *Bartonella* spp. infection is likely a complex interaction that is influenced by both host and organism factors. Lymphadenopathy, endocarditis, myocarditis, and hyperglobulinemia are other well documented manifestations of bartonellosis in cats.[7-10]

As *B. henselae*, *B. clarridgeiae*, *B. koehlerae* are transmitted by fleas, bacteremia and antibody positive rates can be very high. For example, serum antibodies were detected in 93% of cats housed in a North Carolina shelter and *Bartonella* spp. DNA was amplified from the blood of > 50% of cats housed in an Alabama shelter. The majority of these cats were thought to be normal which emphasizes that fever from bartonellosis cannot be documented by test results alone. In one study of pair matched cats with or without fever, serum *Bartonella* antibodies detected by ELISA or Western blot immunoassay were not correlated to the presence of fever.[10] In addition, serum antibody test results are negative in between 3 and 15% of bacteremic cats. Thus, if a cat with fever is to be evaluated for *Bartonella* spp. infection the combination of blood culture or PCR assay on blood, and serologic testing will detect the greatest number of cats that are currently or previously infected (www.dlab.colostate.edu; www.galaxydx.com). Febrile cats that are seronegative and negative for *Bartonella* spp. in blood by culture or *Bartonella* spp. DNA in blood are unlikely to have the organism as the cause of fever.

If fever or other clinical signs from bartonellosis is suspected in a cat, administration of doxycycline or a fluoroquinolone is generally effective. The AAFP Panel Report recommended doxycycline at 10 mg/kg, PO, daily for 7 days as the initial therapeutic trial. If a positive response is achieved, continue treatment for 2 weeks past clinical resolution of disease or for a minimum of 28 days. If a poor response is achieved by day 7 or doxycycline is not tolerated and bartonellosis is still considered a valid differential diagnosis, fluoroquinolones are appropriate second choices. In experimental or field studies, administration of enrofloxacin or orbifloxacin have led to rapid resolution of fever in cats with presumed bartonellosis. Azithromycin is now considered contraindicated because of rapid induction of resistance.[11] The new veterinary fluoroquinolone, pradofloxacin (Veraflox, Bayer Animal Health) is the least likely to cause resistant strains of *B. henselae* and so may be the preferred quiniolone for the treatment of this syndrome.[11] Flea control with imidocloprid containing compounds (Advantage Multi and Seresto collar; Bayer Animal Health) has been shown to block transmission of *B. henselae* amongst cats by *Ctenocephalides felis*.

Borreliosis

Many cats exposed to *Ixodes* spp. in North America and parts of Europe develop antibodies against *B. burgdorferi.*[12] Some cats are also infected by *Borrelia persica* from infestation by *Ornithodoros tholozani* in some parts of the Middle East. Fever can be associated with B. burgdorferi or *B. persica* infections in cats. However, since many cats have exposure to *Ixodes* spp., it can be difficult to determine whether clinical illness is resulting from *A. phagocytophilum* or *B. burgdorferi* or both.[12]

Cats with fever and suspected *B. persica* infections should have peripheral blood smears evaluate for spirochetes and the infection can be confirmed by PCR assay. While not approved for this use, serum from cats with fever and suspected *B. burgdorferi* infection can be screened with a commercially available kit (SNAP4DXPlus, IDEXX Laboratories, Portland Maine, USA) titrated for use with dog sera. However, a positive *B. burgdorferi* antibody assay result only proves exposure, not necessarily clinical borreliosis.

Cats with fever from suspected borreliosis generally respond to administration of doxycycline at 5 mg/kg, PO, twice daily or 10 mg/kg, PO, once daily. The effectiveness of different acaricides for the prevention of transmission of *Borrelia* spp. to cats has not been compared but based on experiences in dogs, all should be effective in cats if used appropriately.

Cytauxzoonosis

Cytauxzoon felis is a protozoal disease of cats in the southeastern, mid-Atlantic, and south-central United States that is often fatal when clinical illness occurs unless appropriate treatment is administered. *Cytauxzoon* spp. infection has also been documented in many European countries but seems less pathogenic than in the USA. Isolates from domestic cats have been genetically similar between studies. Bobcats are usually subclinically affected and may

therefore be the natural host of the organism. Recent genetic analysis performed on *C. felis* from bobcats and pumas suggest multiple strains of the organism exist in wild felids. Domestic cats can be infected by different genotypes, alone or in combinations. The organism can be passed experimentally from infected bobcats to domestic cats by *Dermacentor variabilis* (American dog tick) and *Amblyomma americanum* (Lone Star tick); clinical illness occurs after an incubation period of 5 to 20 days. The majority of cases are diagnosed in April, May and June. After infection, schizonts and macroschizonts form in mononuclear phagocytes. The infected macrophages line the lumen of veins throughout the body. Merozoites released from the infected macrophages infect erythrocytes. Clinical disease results from obstruction of blood flow through tissues by the mononuclear infiltrates and from hemolytic anemia. Domestic cats occasionally survive infection, suggesting that variants that are less virulent to cats also exist. Perinatal infection did not occur from 2 queens to their 14 kittens.

Most cases of cytauxzoonosis are in cats allowed to go outdoors. Fever, anorexia, dyspnea, depression, icterus, pale mucous membranes, and death are the most common clinical findings. A primary differential diagnosis is mycoplasmosis. Ticks are rarely identified on affected cats. Regenerative anemia, pancytopenia, and neutrophilic leukocytosis are the most common hematologic findings; thrombocytopenia occurs in some cats. Hemoglobinemia, hemoglobinuria, hyperbilirubinemia, and bilirubinuria are uncommon. Antemortem diagnosis is based on demonstration of the erythrocytic phase on thin blood smears stained with Wright's or Giemsa stains. Infected macrophages can be detected cytologically in bone marrow, spleen, liver, or lymph node aspirates. The organism is easily identified on histopathologic evaluation of most organs. Serologic testing is not commercially available. PCR can be used to amplify organism DNA from blood and positive test results prove current infection.

Supportive care includes fluid therapy and blood transfusion administered as indicated. Manipulation of the cat should be minimized as stress can potentiate fatalities. Recently, a prospective study compared survival in cats treated with atovaquone at 15 mg/kg, PO, q8h and azithromycin at 10 mg/kg PO q24h to cats treated with imidocarb at 3.5 mg/kg, IM.[13] The survival rates for the atovaquone/azithromycin combination and imidocarb were 60% and 26%, respectively.

Cytauxzoon felis is not known to be zoonotic. The disease can only be prevented by avoiding exposure. Ticks should be controlled, and cats in endemic areas should be housed during periods of peak tick activity. One commercially available flea and tick collar (Seresto, Bayer Animal Health) has been shown to block transmission of *C. felis*.[14]

Ehrlichiosis

Ehrlichia-like bodies or morulae have been detected in peripheral lymphocytes or monocytes of naturally exposed cats in a number of countries including the United States, Kenya, France, Brazil, and Thailand. Researchers in Brazil, North America and Portugal have amplified DNA consistent with *E. canis* from naturally infected cats. However, other studies of cats in endemic areas (Florida and Arizona) have failed to amplify *Ehrlichia* spp. DNA from the blood of cats. In 2 separate experimental studies, we have failed to amplify monocytotropic *Ehrlichia* spp. from blood or detect seroconversion in cats inoculated SQ with different strains of cultured *E. canis* (Lappin and Breitschwerdt, unpublished observations, 2007; Lappin and Little, unpublished observations, 2010). These results indicate the *E. canis*-like DNA amplified from naturally-infected cats may be from a different *Ehrlichia* spp. more infective to cats, not all *E. canis* stains will infect cats, not all cats are susceptible to infection by *E. canis*, or SQ inoculation is not an effective method for infecting cats with *E. canis*. Some cats with suspected clinical ehrlichiosis have seroreacted to *E. canis* or *N. risticii* morulae.

Fever is one of the reported clinical abnormalities detected in cats with suspected ehrlichiosis and so testing may be indicated in these cats. However, a validated serological assay is not currently available and some cats with *E. canis*-like DNA in blood were seronegative.[15] In contrast, most *A. phagocytophilum* infected cats have strongly positive antibody test results. Positive serologic test results occur in both healthy and clinically ill cats, and so a diagnosis of clinical ehrlichiosis should not be based on serologic test results alone. *Ehrlichia* spp. PCR and gene sequencing can be used to confirm infection and should be considered the tests of choice at this time.

Clinical improvement after therapy with tetracycline, doxycycline, or imidocarb dipropionate was reported for most cats with suspected mononcytopic ehrlichiosis.[15, 16] However, for some cats a positive response to therapy was a criterion for the diagnosis of ehrlichiosis. The recommendation of the ACVIM Infectious Disease Study Group is to give doxycycline (10 mg/kg PO q24h for 28 days). For cats with treatment failure or those intolerant of doxycycline, imidocarb diproprionate can be administered (5 mg/kg IM or SQ twice, 14 days apart). Salivation and pain at the injection site are the common adverse effects and imidocarb efficacy is in question for the treatment of canine monocytotropic ehrlichiosis.

Hemoplasmosis

Hemolytic anemia, with or without fever, are the most common abnormalities associated with infection by *Mycoplasma haemofelis*, *'Candidatus* Mycoplasma haemominutum', or '*Candidatus* M. turicensis'. In multiple studies of experimentally infected cats, *M. haemofelis* is apparently the most pathogenic species. Dual infection with hemoplasmas or coinfections with retroviruses may potentiate pathogenesis of disease.[17-20] In one study, cats with chronic *'Candidatus* Mycoplasma haemominutum' infection had more severe anemia and longer duration of anemia when experimentally infected with *M. haemofelis* when compared to cats infected with *M. haemofelis* alone.[17] In one abstract, our research group reported an association between *M. haemofelis* and fever in cats without anemia. Clinical signs of disease depend on the degree of anemia, the stage of infection, and the immune status of infected cats. Direct transmission may occur with the hemoplasmas and so the agents should be on the differential list for cats with a history of fighting.[21]

Diagnosis of hemoplasmosis is based on demonstration of the organism on the surface of erythrocytes on examination of a thin blood film or by PCR assay results. Organism numbers fluctuate and so blood film examination can be falsely negative up to 50% of the time. The organism may be difficult to find cytologically, particularly in the chronic phase. Thus, PCR assays are the tests of choice due to sensitivity.

Doxycycline is often administered as a flavored suspension (to avoid esophageal strictures) at 10 mg/kg, PO, every 24 hours for a minimum of 7 - 10 days. In cats intolerant of doxycycline, enrofloxacin given at 5 mg/kg, PO, every 24 hours for 14 days was tolerated by cats and is equally effective or more effective than doxycycline. Administration of marbofloxacin or orbifloxacin gives similar results. Azithromycin was not effective for the treatment of hemoplasmosis in one study.[17] Pradofloxacin (Veraflox®; Bayer Animal Health) is the only drug proven to eliminate *M. haemofelis* infection in experimentally inoculated cats.[22] Most drug protocols have failed to eliminate infection and so at this time there is no clinical utility to repeat PCR testing. The owners should be warned that recurrences may occur but are unusual.

Feline Rickettsiosis

Rickettsia spp. are obligate intracellular gram negative bacteria that are divided into the spotted fever group and the typhus group. Cats can be infected by *Rickettsia felis* and have been shown to have antibodies against *R. rickettsii*. *Rickettsia felis* DNA has been amplified from *C. felis*, *C. canis,* and *Pulex irritans;* these fleas have a worldwide distribution. *Ctenocephalides felis* is a biological vector for *R. felis*; the organism can be transmitted transovarially and transtadially within the flea. Rickettsial infection is suspected to a cause of fever in cats but this has not been well documented. While we have commonly amplified *R. felis* from *C. felis* (67.4% of flea extracts in one study), we have not amplified the organism from the blood of healthy cats or cats with fever. However, in one study of cats with fever we showed *R. felis* and *R. rickettsii* antibody prevalence rates in cats in the USA to be 5.6% and 6.6%, respectively but neither organism was amplified from blood.[23] These results prove that cats are sometimes exposed to spotted fever group organisms but further data are needed to determine significance of diseases associations. Because clinical illness in cats has not been documented, optimal treatment is unknown. However, based on results in dogs, doxycycline or a fluoroquinolone would be logical choices.

Summary

There are other infectious agents of cats that are either blood borne or associated with vectors that should be on the differential list for cats with appropriate clinical findings and geographical locale including *Francisella tularensis*, *Hepatozoon* spp., and *Yersinia pestis*. Coinfections are common and may potentiate disease.

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The Cushingoid Diabetic: Recognition, Diagnosis, & Management

Audrey Cook, BVM&S, MRCVS, MSc Vet Ed, DACVIM, DECVIM, DABVP (Feline)

Introduction

Cats with diabetes mellitus (DM) and hyperadrenocorticism (HAC; aka Cushing's) present some unique challenges. This lecture will review the clinical signs of HAC, how to establish a diagnosis, and management strategies for cats with both pituitary dependent disease (PDH) and HAC secondary to a functional adrenal tumor (AT).

Etiology of hyperadrenocorticism

Most cats with spontaneous HAC have an underlying pituitary tumor (80%; usually an adenoma), with inappropriate secretion of adrencorticotrophic hormone (ACTH) and secondary hypercortisolemia. The minority have an AT; in contrast to dogs, these tumors often secrete more than one adrenal hormone and affected cats may show signs related to concurrent hyperaldosteronism or hyperprogesteronism. In addition, Cushingoid signs can occur in the absence of actual hypercortisolemia if the AT product is able to bind to intracellular glucocorticoid receptors.[1] Tumors may be malignant carcinomas or benign adenomas, with about an even split between the two possibilities.

Recognizing HAC in the diabetic cat

Although uncommon (<200 cases are reported in the peer-reviewed literature), Cushing's syndrome is a well-recognized cause of insulin resistance in cats, and this possibility should be considered if a feline patient is poorly responsive to insulin. As a general rule, 'insulin resistance' is defined by a blood glucose >300 mg/dL (16.6 mmol/L) despite an insulin dose ≥ 5 U/injection.[2] Bear in mind however that a cat may have HAC without overt insulin resistance, and we now routinely diagnose HAC in non-diabetic cats.

The clinical signs of spontaneous HAC in cats can be subtle and are quite different to those noted in dogs. For example, non-diabetic HAC cats are not predictably polyuric, polydipsic or polyphagic. Of course, a poorly regulated DM cat will have all three of those clinical signs! As a general rule, HAC will cross my mind if I am dealing with a difficult diabetic, or if the physical examination is suggestive of this condition.

Signalment

Cats with HAC have a mean age of 10-11 years at the time of diagnosis. Males may be slightly overrepresented.[3,4]

Physical examination

Changes in the physical examination are often the first suggestion of feline HAC. Affected cats will develop visceral adiposity and lose muscle strength, resulting in a 'pot-bellied' appearance. This can be quite dramatic. A plantigrade stance may be noted, although again this may reflect a peripheral neuropathy secondary to hyperglycemia or hypokalemia rather than tendon weakness from hypercortisolemia alone. Skin changes may be dramatic and are often the most useful diagnostic clue. Alopecia (usually fairly symmetrical) is often noted, particularly on the ventrum, and the skin if often thin with poor elasticity. Failure of hair regrowth after clipping may be an early sign of HAC. Skin infections may be reported. Overt skin fragility with tearing is noted in the minority of HAC cats (<1/3 of reported cases) but is essentially pathognomonic for this condition. Weakening of the cartilage of the ears may result in folding of the ear tips (although this appears to be more common in cats with iatrogenic rather than spontaneous HAC). Overall, cats with HAC have a generally decrepit appearance, with weight loss and signs of cachexia.

Routine laboratory findings

Hyperglycemia is expected in the Cushingoid diabetic, although this can be mitigated by hefty doses of insulin. Other changes noted on routine labwork may include increases in serum alkaline phosphatase (ALP) and/or alanine aminotransferase (ALT) activity. Increased ALP activity likely reflects some degree of hepatic lipidosis, as cats do not have a glucocorticoid induced isoenzyme. Hypercholesterolemia is common and is likely associated with poorly regulated DM rather than HAC. Unless there is concurrent hyperaldosteronism, electrolytes are normal.

Results of the complete blood count are often unremarkable, as cats do not predictably manifest a 'stress leukogram'. Interestingly, anemia is not uncommon in cats with HAC (in contrast to canine patients).[3-5]

Urine specific gravity will be impacted by concurrent glycosuria; HAC *per se* is not associated with a decrease in renal concentrating ability in cats. Findings suggestive of a urinary tract infection may be noted. However, a urine culture is generally considered appropriate irrespective of findings on sediment exam.

Serum fructosamine concentrations will reflect the degree of glycemic control but are generally above the reference range. Serum thyroid concentrations may be subnormal (euthyroid sick/secondary hypothyroidism) but are usually within the reference range.

Imaging studies
Abdominal radiographs provide limited information in cats with HAC, although a mass effect (+/- calcification) may be noted in patients with a large AT.

Ultrasonography is much more useful, as the size, shape and symmetry of both adrenals can be determined. An experienced sonographer with high frequency probe should be able to identify and measure both glands. Normal dimensions for the width of the feline adrenal gland are 0.29 – 0.53 cm.[6] Most cats with PDH have overtly large or 'plump' adrenals; however, the possibility of HAC should not be discounted on the basis of normal dimensions.

Differential diagnoses
There are very few other explanations for the physical changes associated with HAC in the cat. An abdominal mass or ascites are considerations in cats with overt abdominal distention. Differentials for a plantigrade stance include hyperaldosteronism or a peripheral neuropathy.

Differentials for feline insulin resistance include systemic inflammatory disorders, hyperthyroidism, exogenous glucocorticoids or progestogens, and acromegaly. The latter is the most likely differential in a cat with overt insulin resistance but a robust body condition score (+/- progressive weight gain) and a normal dermatologic examination.

Confirming hyperadrenocorticism
Confirming HAC can be challenging, as non-adrenal illness will impact test results. It is also important to remember that the test protocols used in dogs are not appropriate for cats. Bear in mind too that "Cushing's" may arise from the secretion of a hormone other than cortisol by an AT, or other adrenal hormones may be released along with cortisol. Specific testing (e.g., baseline aldosterone measurements, fludrocortisone suppression test, extended adrenal panel at U of Tennessee) may therefore be necessary to fully identify the function of these tumors. Diagnostics may need to be limited in cats with skin fragility, as handling for venipuncture etc. can be problematic.

Urine cortisol: creatinine ratio (UCCR)
There is relatively little information regarding this test in cats but it does appear to be a fairly useful way to exclude HAC, meaning that UCCRs below the cut-off established by the laboratory makes this diagnosis very unlikely.[7] Ideally, two or three urine specimens should be collected in the home to improve reliability. However, a positive result on this test is not sufficient evidence to start treatment, and additional endocrine testing is generally needed (although I might start treatment based on elevated UCCRs in a cat with skin fragility and skip additional testing).

Low dose dexamethasone suppression test (LDDST)
This is widely regarded as the best confirmatory test for HAC in both dogs and cats, although results can be substantially impacted by stress or non-adrenal disease. However, the dose of dexamethasone required to consistently suppress cortisol release in normal cats is 10-fold higher than in dogs, i.e., 0.1 mg/kg IV.[4] This is administered following collection of the baseline blood sample; additional samples are then collected 4 and 8 hours later. An 8-hr cortisol ≥1.4 µg/dL (40 nmol/L) is generally considered to be consistent with a diagnosis of HAC[4]; practitioners should however refer to the data provided by the laboratory used.

ACTH stimulation test
Most internists have limited confidence in the ACTH stimulation test as it lacks both sensitivity and specificity; only 56% of cats with HAC were identified using this test in a recent study.[5] However, it is a reasonable choice if a cat is clearly stressed by being in the clinic, as short-term psychological upset should not impact results. A baseline serum sample is collected, and synthetic ACTH is given. There are various protocols, and the timing of the subsequent venipunctures is affected by the route of administration.[8] I recommended giving 125 µg of cosyntropin (Cortrosyn®) IM, with blood collection at 30, 60 and 90 minutes; other sources prefer IV administration with samples collected at 60, 90, and 120 minutes. Practitioners are advised to consult with their laboratory to see which protocol is preferred. This dose of cosyntropin is likely more than necessary, and studies to determine the minimal dose needed for maximal adrenal stimulation in cats are clearly needed. A post-ACTH cortisol >19 µg/dL (525 nmol/L) at any time point is generally consistent with a diagnosis of HAC (but refer to your laboratory's reference range).[4]

Pituitary imaging
Although there is limited data regarding the sensitivity of both CT and MRI for the identification of a pituitary mass in cats with PDH, both imaging modalities appear useful. In one study, every cat with a final diagnosis of PDH had a visible mass on advanced imaging.[9] Interestingly, a pituitary mass in an insulin-resistant cat is most likely to be a

growth hormone secreting tumor (i.e., the cat has acromegaly) so simply finding a pituitary lesion is not enough to prove underlying HAC. However, finding a mass in a cat with clinical signs and endocrine test results suggesting HAC is very strong confirmatory evidence of this diagnosis.

Differentiating PDH from AT

In my practice, I routinely perform an ultrasound exam before pursing any endocrine testing in cats with insulin-resistant DM; this is an excellent way to identify an AT. In one study of 32 cats with HAC, ultrasonography correctly differentiated between the two forms in 93% of cases.[5]

Close evaluation of the LDDST results may permit the identification of cats with PDH; this is supported by a >50% decrease in cortisol from the baseline value at the 4-hr or 8-hr mark (approximately 50% of cases), or an absolute value <1.4 µg/dL (40 nmol/L) at 4-hrs (uncommon).

Although some data has been published regarding the measurement of feline endogenous ACTH, this test is not routinely available. Similarly, measurement of ACTH precursors may also be helpful, but is also not available.[10]

The high dose dexamethasone suppression test (1.0 mg/kg IV) may also be considered, although less than 50% of cats with PDH meet the criteria for suppression (i.e., ≥ 50% decrease in cortisol or a 4-hr or 8-hr value <1.4 µg/dL/40 nmol/L).[4] This test has effectively been replaced by ultrasonography, and most internists have never performed this in a feline patient.

Management of HAC

There are several challenges related to the management of a cat with DM and HAC. These include changes in insulin sensitivity as hypercortisolemia is reversed; the relative unpredictability of medical options for HAC in cats; and the need to address co-morbid conditions such as skin fragility and hypertension (reported in ≈ 20% of cases). Hypoglycemia is a killer, so owners must be encouraged to monitor blood glucose at home (intermittent curves or an interstitial glucometer such as the FreeStyle Libre®) and empowered to decrease insulin doses as appropriate.

Surgical treatment

Surgery is the treatment of choice for cats with an AT.[4] Abdominal CT may be necessary to facilitate surgical planning. Peri-operative complications are to be expected, and an experienced surgeon with appropriate ICU facilities are necessary. Cortisol supplementation will be necessary immediately following removal of the affected gland but can then be tapered over the next few weeks. Reported outcomes for feline adrenalectomy are fair; in a recent report of 26 cats with various types of adrenal tumors (not just ones causing HAC), 23% died in the peri-operative period but almost 50% were alive at 12 months.[11]

Bilateral adrenalectomy has been reported as an option for cats with PDH (prior to the advent of trilostane).[12] Outcomes were fair, and insulin therapy was discontinued in 4/6 cats.

Medical therapy

Trilostane has shown more promise for the management of feline HAC than any other medical therapy to date, although only a small number of cases have been reported.[13,14] This drug is a reversible inhibitor of a key enzyme needed for cortisol production, and its effects are both transient and dose-dependent. Although I routinely use trilostane q24 hr in dogs, I always split the dose in diabetic patients, as it makes sense to make their endocrine events (cortisol and insulin) as well balanced as possible. Reported effective doses range widely in cats, and likely reflect differences in drug uptake and metabolic effects within the individual patient. I tend to start conservatively, with a 1-1.5 mg/kg PO BID plan. As in dogs, there is little consensus about optimal monitoring methods; it has been suggested that a 4-hr post ACTH cortisol concentration between 1.8 and 5.5 µg/dL (50 - 150 nmol/L) indicates adequate control in cats.[14] Bear in mind however, that (as in dogs), the clinical examination and signs are likely the best reflection of the efficacy of therapy. In one report of 15 cats, the median survival time with trilostane was 617 days.[14] Interestingly, only 9 of these had concurrent DM; insulin needs decreased substantially in 6/9 but all of the cats remained insulin-dependent/overtly diabetic.

Radiation

Advances in the field of radiotherapy have made this a more realistic option for cats with PDH, as treatment courses can be shorter. However, only a small number of cats with PDH and DM have been reported, and determination of outcome is difficult as some had overt neurologic signs, radiation methods and protocols vary substantially (fractionated versus stereotactic), and many of the case series include cats with acromegaly.[15,16] Although some cats become insulin independent, the majority do not undergo diabetic remission; however clinical signs (related to DM +/- neurological issues) may be mitigated. Owners need to be sure they understand the likely outcomes, including the risks of early or late onset side effects.

Hypophysectomy

Removal of the pituitary tumor is the treatment of choice in people with PDH and is likely to become more routine in feline patients over the next decade as more institutions begin to offer this procedure. Four of 7 cats in one case series had concurrent DM; HAC resolved in all 5 cats surviving the peri-operative period and all surviving DM+HAC cats became insulin-independent.[17] Treated cats will need life-long glucocorticoid (prednisolone) and thyroid supplementation. Transient diabetes insipidus is managed with desmopressin.

Summary

Practitioners need to be aware of the clinical manifestations of HAC, and look for these in cats with DM. Early recognition of HAC may facilitate successful intervention, either with trilostane, adrenalectomy or hypophysectomy. Cats with well-established HAC are challenging to manage, as skin fragility and general debility become problematic. A sound understating of how to investigate adrenal function is needed, so that appropriate testing is performed. Addressing HAC in the diabetic is likely to impact glycemic control, so owners must be proactive in the management of their cat's changing insulin needs.

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NOTES:

Managing IBD in the Diabetic Cat - Part 1: Challenges

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Introduction

Inflammatory bowel disease (IBD; also known as chronic inflammatory enteropathy) is a common condition in cats, and is thought to reflect a disruption in the normal interactions between dietary components, the gastrointestinal (GI) microbiome, and the mucosal immune system.[1] Clinical signs can be mild, intermittent and of variable severity, and include changes in appetite, weight loss, vomiting and diarrhea. Diagnosis requires the exclusion of other causes of enteropathy and the identification of an increased number of non-neoplastic immune cells within the GI tract. Cats may show a clinical response to a diet change (aka food responsive enteropathy), antimicrobials (aka antibiotic responsive enteropathy), or immunomodulators (aka idiopathic / steroid-responsive IBD). Many cats with IBD have concurrent inflammation of the pancreas[2]; it is unclear if this plays a direct causative role in the development of diabetes mellitus (DM), but insulin resistance secondary to inflammatory mediators certainly impacts β cell function.[3] Although the prevalence of concurrent IBD and DM is unknown, clinical experience suggests this is a fairly common occurrence and it certainly presents some specific challenges.

In Part 1 of this 2-lecture series, we will discuss key concerns related to cats with IBD and DM and outline a logical diagnostic approach from both a medical and nutritional standpoint.

Recognizing IBD in the Diabetic Cat

Some diabetic cats with concurrent IBD are easy to identify, as they vomit frequently or have overt changes in stool volume, frequency and consistency. However, not all cats with IBD have overt GI signs; some are hyporexic, some are polyphagic, and some simply fail to maintain an adequate body condition despite apparently adequate caloric intake. A poor appetite is unexpected in a non-ketotic diabetic, but both polyphagia and weight loss occur routinely in cats with poorly regulated DM; the possibility of IBD may therefore be overlooked. Concurrent IBD should be considered if markers of glycemic control (e.g., water intake, blood glucose curves or serum fructosamine concentrations) are acceptable, but the patient is taking in more calories than expected or fails to maintain an acceptable weight or body condition score.

Intestinal dysfunction can also impact glycemic control and the effects of exogenous insulin, as the GI tract secretes several hormones that influence GI motility, nutrient digestion, food intake/satiety and glucose homeostasis. Key players from this perspective include the incretins, particularly glucagon-like peptide 1 (GLP-1). This hormone is made by specialized cells within the brush border in response to the arrival of particular nutrients and plays a key role in energy regulation. Essentially, the arrival of food (particularly protein and fat) triggers the secretion of GLP-1; this turns off hepatic gluconeogenesis, readies the body for the arrival of calories and insulin, and suppresses further food intake.[4] Disrupted incretin production secondary to IBD may explain why some diabetics have an inconsistent response to the same dose of insulin: delayed gastric emptying secondary to IBD may result in hypoglycemia, whereas compromised GLP-1 secretion may cause hyperglycemia and hunger.

Although hypoalbuminemia is relatively uncommon in cats with IBD, increased protein turnover secondary to chronic GI loss is a likely component of this condition in many patients. A healthy liver can compensate for moderate albumin loss and serum concentrations may therefore remain within the reference range. However, the shortened half-life will decrease fructosamine concentrations. Therefore, IBD should be considered in a cat with clinical signs suggesting poor diabetic regulation (i.e., persistent polyuria and polydipsia) but with a fructosamine concentration within the target range.

Patient evaluation

A discussion of the diagnostic work up for IBD is beyond the scope of this session, but would routinely include CBC, chemistry panel, uranalysis, fecal floatation +/- molecular testing for specific pathogens, measurement of thyroxine, trypsin-like immunoreactivity, pancreas-specific lipase immunoreactivity (fPLI), folate, and cobalamin, abdominal ultrasonography and collection of intestinal tissue(s). However, there are some specific concerns related to cats with concurrent DM.

Weight loss, body condition score, muscle condition score

While pet owners are somewhat likely to present a cat for evaluation of vomiting, diarrhea, and even inappetence, they frequently fail to observe subtle, chronic weight loss in cats. An objective review of a patient's medical record with respect to weight change is key to assessment, regardless of the pet owner's impressions of weight stability-especially if the patient is presented for evaluation of the more overt clinical signs. If medical history includes body

condition scoring (BCS), this is helpful, but may be less so when performed by different clinicians unless weight change is dramatic or there is are efforts to standardize BCS assessment within a practice. Regardless of inter-observer variation, BCS is crucial to include in a patient's assessment. While muscle condition scoring (MCS) is related to BCS (muscle wasting is a feature of the lower body condition scores), it should be considered separately. Muscle wasting is common in middle-aged and older cats; overweight and obesity makes this more difficult to detect[5] (and nearly impossible for most pet owners to notice), but its presence is key to a nuanced assessment, especially in patients with multiple comorbidities.

Dietary history
Caloric intake
Especially in cats, where pathognomonic clinical signs are rare, review of a complete diet history is another means of putting the available data for a patient to better use in fully assessing a patient. First, having details on specific diet and quantity consumed, especially over time, allows for determination of whether caloric intake is appropriate at the time, as well as whether there has been a change in intake. It is worth noting that in patients whose diet history includes many diet changes, commercial cat diets vary widely in caloric density (calories per unit), so an increase or decrease in volume consumed does not always represent an increase or decrease in caloric intake. On a related note, many pet owners who have struggled with maintaining intake in an inappetent patient overestimate the significance of the amount consumed when there is a bit of success. While it's important to celebrate small victories in these cases, it is important to remain objective about the calories consumed. Presenting this to the pet owner as a percentage of calculated maintenance requirement can help put this into perspective.

Caloric distribution
Having data on specific diet and amount consumed is most informative, but not always realistic, especially in multi-cat (more frequently fed ad libitum) households. Even without intake data, having the correct name and manufacturer of each product fed is informative, as it allows for determination (or at least estimation) of the caloric distribution (percentage of calories from protein vs. fat vs. carbohydrate and ingredient declaration. Knowing that a patient's current status is their manifestation of response to a high-protein, high-fat, and low-carbohydrate vs. a diet moderate in protein, fat, and carbohydrate is relevant to planning a next therapeutic move. Manufacturers can also be contacted for more specific information such as concentrations of specific nutrients. Commercial diet formulations frequently, so it is incredibly difficult for organizations not associated with the diet manufacturer to maintain a reliable database on commercial diets. Reference to the product packaging and manufacturer for further detail is recommended over reliance on websites with product comparison data.

Ingredient declaration
Especially when chronic gastroenteropathy is on a patient's differential list, diet history is also essential to planning therapy, as this allows assessment of a patient's previous ingredient exposure. Notable in the current pet food marketplace is an abundance of over-the-counter diets that include venison, duck, and other ingredients commonly included in therapeutic diets formulated for cats with adverse food response. Concurrently, there is the marketing strategy that these ingredients, despite being included along with common pet food ingredients, are therapeutic in patients with gastrointestinal disease. Well-intentioned pet owners may trial these diets in hope of resolution of symptoms; the result more frequently being exposure to a previously-novel ingredient without elimination of more-likely-problematic ingredients. The prevalence of these diets in the marketplace has led to the scenario where for many patients, "common" protein sources such as beef and pork are actually novel, highlighting the importance of a detailed diet history in each patient and assessing each as an individual. When trying to determine the full list of dietary antigens to which a patient has exposure, questioning pet owners using several different phrases referring to treats, scavenged items, table foods, toothpastes, flavored medications, items used to deliver medications is helpful, as many pet owners don't actually consider these items as part of the diet.

Concurrent pancreatitis
Feline pancreatitis is a common but poorly understood condition. Necropsy studies suggest that chronic inflammation can be found in more than 50% of older cats, although not all cats manifest clinical signs.[6] As pancreatitis has been associated with IBD and may impact glycemic control in cats with DM, it is prudent to screen cats for this condition.[7] Changes to the pancreas may be noted ultrasonographically, although this diagnostic modality may have limited sensitivity. Most internists rely on measurement of serum fPLI to identify pancreatic inflammation, recognizing that this may not correlate directly with clinical signs. In one study, fPLI concentrations in cats with DM (n=29) were higher than non-diabetic controls (n=23) and correlated weakly with serum fructosamine levels. However, there were no significant differences in the prevalence of GI signs between the two groups of cats.[8]

Other diagnostic considerations
A definitive diagnosis of IBD requires histopathological confirmation of GI inflammation; biopsies can be collected either endoscopically or via laparotomy. Endoscopy is associated with a shorter recovery time and less patient

discomfort and is the preferred method for most specialists. Although some practitioners are reluctant to anesthetize a diabetic, most patients handle this well and poorly regulated DM is not a reason to avoid establishing a diagnosis. There is little consensus about optimal anesthetic protocols, but current recommendations include the administration of a small meal along with half the usual amount of insulin a few hours before induction, and the provision of a small amount of food as soon at the cat is sternal and able to eat.[9] Blood glucose (BG) should be checked every 30 minutes during anesthesia and hourly during the recovery phase.

In some cases, an owner may decline GI biopsies, requiring the clinician to make a presumptive diagnosis of IBD. If this is the case, cats must be screened carefully for 'look alike' infectious disorders such as histoplasmosis.

Management considerations

Food type

Commercial canned

For a number of reasons, commercial canned diets are often the most beneficial choice for feeding a diabetic cat in general. Their polyuria predisposes to dehydration, and while feeding a canned diet is expected to result in decreased voluntary consumption of free water, it increases total moisture intake in cats.[10] Additionally, weight loss plans in overweight and obese cats are often easier to execute when using canned diets, as the increased moisture increases satiety[11], and feeding a canned diet usually forces the household into meal-feeding (as opposed to ad libitum feeding of commercial dry diets).

Commercial dry

Commercial dry diets tend to be higher in carbohydrate (a requirement for their processing), though there are a few that fall within recommendations for feeding diabetic cats. As long as cats tolerate their ingredients well and have adequate diabetic control when fed these diets, their appropriateness falls to weight management-related considerations and practicality. For cats who need to gain weight, for cats of ideal BCS, for households where ad libitum feeding is required, or overweight/obese cats whose weight loss plan is proceeding appropriately using dry diets these can be appropriate. Worth noting is that commercial dry diets formulated for diabetic cats are generally very energy-dense- meaning that volume per feeding is small, which can be problematic in a weight loss plan. None of the commercial therapeutic dry diets formulated for diabetic cats have modifications for adverse food response. Weight management considerations as described above are also relevant as preventative considerations when initiating steroid therapy for IBD, as polyphagia can be anticipated.

Other formats

While many cats have strong preferences for either dry or canned commercial diets and refuse other formats, other high-moisture formats such as balanced home-prepared or commercial fresh or frozen diets are also reasonable to consider for diabetic cats if cat and owner are amenable. Raw meat based diets are not recommended due to considerations for contamination with pathogenic microorganisms, particularly in this immunocompromised patient population. For cats currently "doing well" on raw meat-based diets, the diet should be evaluated to determine nutritional parameters driving either real or perceived benefits so that these can be replicated in a diet with lower risk.

Nutritional parameters

Recommendations for feeding diabetic cats, especially when the goal is to achieve diabetic remission, include feeding a low-carbohydrate (</=12% of calories from carbohydrate) diet[12]. Most diets that meet this criterion are canned. There are both commercial over-the-counter and therapeutic diets that can achieve this. It should not be assumed that because one product in a manufacturer's product line meets this criterion that others do as well. Additionally, because guaranteed analysis provides minimum and maximum percentages of protein, fat, crude fiber, and moisture, rather than actual percentages (and there are significant differences between these values); and because crude fiber a is highly inaccurate of indigestible carbohydrate in pet food, conversion of a product's guaranteed analysis to caloric distribution using modified Atwater factors (3.5, 8.5, 3.5 kcal per gram of protein, fat, carbohydrate; respectively) should be used as a tool for screening diets for consideration, rather than deciding whether or not to feed a particular product. If this conversion supports a useful caloric distribution, contacting the manufacturer for typical analysis data (and confirmation that the data is current) is recommended.

Many clinicians report that fat restriction is not helpful for management of cats with pancreatitis, though further study is required. Similarly, dogs with lymphangiectasia as a component of their IBD are fed fat-restricted diets. While lymphangiectasia is reported as a finding in cats with gastrointestinal disease, effects of nutritional modifications to accommodate fat malabsorption are not reported.

Food frequency

Reasonable, logical, arguments can be made for allowing a cat to "graze" throughout the day, and for twice-daily meal feeding[12]. Household logistics, and not what is medically ideal may have to dictate the feeding schedule, and medical therapy may require adjustment to accommodate the feeding schedule that is practical given the diet, owner,

and patient factors at play. Restricting access to other food, preventing others from eating the patient's food, and ensuring the patient eats the appropriate amount consistently and with consistent timing is likely more important than adhering to a particular schedule.

Diet ingredients

While diabetes does not indicate diet selection based on ingredients, food-responsive enteropathy and IBD do. Adverse response to food antigens is the result of immune dysregulation that appears to be associated with time and repeated antigen exposure. The most common antigens associated with proven adverse food response in cats are relatively common pet food ingredients, so the frequency likely has more to do with exposure than antigenicity, again highlighting the importance of individualized nutritional assessment. Eliminating all ingredients to which a patient has previous exposure or feeding a hydrolyzed-protein diet, assessing the response, and re-introduction of single-ingredient food items to determine to what items the patient responds is the most straightforward way to not only definitively diagnose adverse food response, but also determine to what items the patient responds adversely. There are, however, other means to this end, though they require additional time and consideration in formulating the plan. When antigen exposure is extensive (thus limiting options for "novel"), or no diets appropriate for adverse food response are appropriate for the patient's needs as a diabetic, a trial of a limited- (but not necessarily novel- or hydrolyzed-) ingredient diet that is otherwise appropriate for the patient's needs, followed by assessment of effect is reasonable. If the result is favorable, no further work may be required, and re-introduction of single-ingredient food items to determine non-tolerated items is reasonable. If the result of this trial is not favorable, a trial with a second limited-ingredient diet (preferably with different ingredients than the first) is reasonable. Equivocal results are more difficult to interpret with this approach.

Nutritional supplements

Dietary fiber

Supplemental dietary fiber may be beneficial related to treatment of both diabetes and chronic enteropathy. The addition of indigestible carbohydrate may reduce glycemic effect of feeding, particularly in diets that are higher in carbohydrate than ideal for diabetic cats. When low-carbohydrate, high-protein, high-fat diets are fed, the majority of the patient's blood glucose is derived from gluconeogenesis, rather than absorption from diet, so this effect would be expected to be minimal in these diets. Dietary fiber can also be useful as a modulator of stool quality and gastrointestinal transit time, so its inclusion for management of chronic enteropathy is reasonable[1]. Further, a prebiotic effect of supporting populations of beneficial GI microbiota, and promoting microbial diversity, may be achieved, particularly with the inclusion of soluble dietary fiber. With consideration for the diabetic cat with IBD, commercial "high-fiber" diets are not formulated with a low-carbohydrate caloric distribution, nor are they formulated with likely-novel or hydrolyzed ingredients, so may be of limited use. However, supplementation of an otherwise-appropriate diet with insoluble, soluble, or mixed (soluble and insoluble) dietary fiber is reasonable. Different fiber types have varying effects in individual patients, so experimentation with each category may be required to achieve desired effect. Inclusion of, and changes to, dietary fiber supplementation may cause a difference in glycemic response to food, so adjustment of medical therapy and monitoring may be required when these changes take place.

Long-chain omega-3 polyunsaturated fatty acids

Therapeutic use of these fatty acids has not been extensively studied. Large doses can be associated with adverse effects on immune parameters and platelet function. A dose of 75 mg/kg BW (kg)^(2/3) EPA+DHA[13] is generally considered safe and is frequently used to achieve "general anti-inflammatory" goals. As long as the cat does not find the addition of fish oil aversive, the supplement is 100% fat, so its inclusion doesn't interfere with diabetic management goals. High-quality products are expected to be purified and not to contain protein components, so triggering an immune-driven response is not likely. Generally, this is not included at the expense of palatability.

Probiotics

The inclusion of beneficial microbes as a diet supplement is reasonable in cats with chronic enteropathy[1], though strong evidence for benefit is lacking. Initiation of this strategy at a time point when effects of other therapies have been determined is recommended. Many commercially-available probiotic supplements are flavored, so could potentially introduce an antigen problematic to a cat with IBD.

Insulin requirements and glucose monitoring

Many cats with IBD have a fluctuating appetite; this can be very problematic in cats with concurrent DM as the insulin dose may need to be adjusted on a day-by-day basis. As many cats are on small doses of insulin (often just 1-2 U/dose), titrating the dose based on estimated intake can be challenging and clients will need clear guidance on how much to give. It is always prudent to be cautious; it takes much less insulin to prevent ketosis than to achieve euglycemia, so it may be necessary to accept some degree of hyperglycemia in order to reduce the risk of an insulin overdose. Owners must be empowered to decrease the insulin by up to 50% if intake is poor but should not withhold insulin for more than 24 hours unless instructed to do so by a veterinarian.

At-home BG monitoring is strongly encouraged; this lets owners make informed decisions about insulin needs and reduces the risk of hypoglycemia. As unobserved hypoglycemia is one of the major worries expressed by diabetic pet owners, the ability to recognize this and intervene can be very reassuring. At-home spot checks of BG are helpful, but many practitioners recommend continuous interstitial glucose monitoring for vulnerable patients. These devices (discussed in the next lecture) are inexpensive and generally well-tolerated.

Appetite, nausea and vomiting
A pro-active stance regarding the use of appetite stimulants and anti-emetics is strongly encouraged; it is better to preempt these issues rather than manage them in a compromised patient. As cats with DM have a substantial increase in urine output, they are more vulnerable to dehydration (+/- electrolyte disorders) secondary to vomiting or diarrhea than non-diabetic cats.

In some cats, a feeding tube may be the only way to ensure appropriate food intake (both type and amount). An esophagostomy tube (e-tube) can be quickly placed during diagnostics for IBD and used as necessary during the initial treatment phase.

Medical management of IBD
Many of the drugs (e.g., glucocorticoids, cyclosporine) used to address idiopathic/steroid responsive IBD can impact glycemic control. This can be anticipated and mitigated by logical adjustments to insulin doses, and concerns about diabetic dysregulation should not preclude the use of necessary immunomodulators. However, dose formulations and frequency should be considered carefully. For example, depository methylprednisolone products are a poor choice when compared to oral prednisolone, as the latter can be adjusted based on clinical response whereas the depository product will wear off at a somewhat unpredictable rate and have a variable impact on insulin requirements. Although some immunomodulators (e.g., chlorambucil) have little impact on insulin sensitivity, they may have other side effects, and practitioners will need to carefully consider all options.

Summary
Concurrent IBD and DM can be challenging, and practitioners, and affected cats will need a thorough assessment and a tailored treatment plan. Specific management strategies for these patients will be discussed in Part 2 of this lecture series.

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Managing IBD in the Diabetic Cat – Part 2: Strategies

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Introduction

In the second part of this 2-lecture series, we will discuss ways to optimize the management of the diabetic cat with inflammatory bowel disease (IBD). Attendees and readers should refer to Part 1 for more background, and an outline of how best to evaluate the cat with diabetes mellitus (DM) and concurrent IBD.

Feeding management

Implementation of a feeding plan that incorporates the relevant features (see Part 1) of feeding the diabetic cat with IBD is a challenge and may be more so if the patient has additional comorbidities with potentially-conflicting nutritional management strategies, such as chronic kidney disease. Customization is key. Considering pet owner-related factors and preferences is a necessity. Based on the patient's nutritional assessment[1] and medical evaluation, a "wish list" of features of an ideal nutritional plan can be assembled.

Commercial diets

Most pet cats in the US eat either dry or canned commercially-prepared diets. Cats develop preferences for specific textures and flavors early on, and changing diets or diet format can be challenging. It may be an overt limitation on diet choice, depending on the owner's willingness/ability to implement change. However, with time and owner willingness/dedication, as long as cats are feeling well when transition is attempted, changes can usually be made.

*Dry diets for diabetes**

Of the commercial therapeutic dry diets formulated for cats with diabetes by major manufacturers, the lowest carbohydrate content available is 11% of calories (Purina Proplan Veterinary Diets DM Dietetic Management dry; contains poultry, soy, corn), followed by 16% (Hill's Prescription Diet m/d Feline dry; contains chicken, corn, rice, wheat, pork), and 25% (Royal Canin Veterinary Diet Glycobalance; contains chicken, corn, barley, wheat, tapioca, soy).

*Dry diets for IBD (limited ingredient and hydrolyzed diets)**

Of the commercial therapeutic dry diets formulated for cats with adverse food response by major manufacturers, the lowest carbohydrate content available is 28% (Hill's Prescription Diet d/d Duck & Green Pea Formula; contains pea, duck). Other therapeutic venison-, duck-, rabbit, and hydrolyzed-protein diets range from 29-37% of calories from carbohydrate, making these generally less ideal diets for diabetic cats (at least when remission is a goal).

*Canned diets for diabetes**

Of the commercial therapeutic canned diets formulated for cats with diabetes by major manufacturers, the lowest carbohydrate content available is 11% of calories (Purina Proplan Veterinary Diets DM Dietetic Management canned; contains chicken, beef, pork, wheat, soy), followed by 13% (Hill's Prescription Diet m/d; contains pork and soy), and 14% (Royal Canin Veterinary Diets Glycobalance; contains pork, chicken, wheat).

*Canned diets for IBD (limited ingredient diets)**

Of the commercial therapeutic canned diets formulated for cats with adverse food response by major manufacturers, the lowest carbohydrate content available is 15% of calories (Royal Canin Veterinary Diets Selected Protein PR canned; contains rabbit, pea), followed by 16% (Royal Canin Veterinary Diets Selected Protein PD; contains duck, pea, and Hill's Prescription Diet d/d Venison Formula; contains venison, pea), 17% (Hill's Prescription Diet d/d Duck Formula- note that this is a different diet than "duck and green pea formula"; contains duck, pea). Other therapeutic venison-, duck-, and hydrolyzed chicken diets range from 24-34% of calories from carbohydrate.

Home-prepared diets

Balanced home-prepared diets offer the most flexibility in terms of ability to customize diet to the patient's ideal nutritional parameters and ingredients. Acceptance on the part of the cat, and logistics of preparation on the part of the owner (both ability and willingness) are significant limitations to this option. Even if this is agreed upon (by veterinarian and owner) that this is the goal/plan, an interim plan may be needed to keep the cat eating something it tolerates while transition is being made. If this option is considered, providing a balanced diet formulated by a nutrition service that includes a Board Certified Veterinary Nutritionist™ (nutrition services listed at acvn.org, BalanceIT.com, petdiets.com) is essential, as it has been shown that cat diets obtained from other sources are likely problematic.[2]

Making a choice
While the group of canned diets formulated for adverse food response all exceed the recommended carbohydrate intake for diabetic cats,[3] this group is generally most promising in terms of managing gastrointestinal disease without complicating diabetic management. If a cat owner has been able to isolate ingredients to which the cat responds adversely, additional therapeutic diets (usually those formulated for gastrointestinal disease in general) or over-the-counter diets may be appropriate if they exclude the offending antigen, but inclusion of contaminant ingredients not listed in the ingredient declaration is a concern.[4] Managing a diabetic cat with IBD is a labor-intensive endeavor for most pet owners. While home-prepared diets may offer the appealing option of being able to be fully customized to the patient's needs, transitioning a dry- or canned-food-acclimated cat to a home-prepared diet, and then faithfully and reliably preparing food with the full responsibility for food safety and nutrition placed on them, many pet owners (quite reasonably) don't pursue this option due to practicality.

Nutritional supplements
Vitamin B12
Vitamin B12 (cobalamin) absorption in the cat, in addition to adequate dietary cobalamin, requires gastric acid production, exocrine pancreatic synthesis of intrinsic factor, and ileal expression of the B12-intrinsic factor receptor. Disease affecting the stomach, pancreas, and ileum all can impede vitamin B12 absorption. In addition, gastrointestinal disease shortens the half life of vitamin B12 by decreasing enterohepatic recirculation, thus effectively increasing the requirement in patients with gastrointestinal disease. Because of this "failure" of enteral absorption of vitamin B12, parenteral administration of 250 mg/cat/week subcutaneously is recommended for hypocobalaminemic cats[5]. Failure to correct hypocobalaminemia is known to result in delayed clinical recovery despite otherwise appropriate therapy.

Folate
Compared to vitamin B12, folate absorption is relatively simple; dietary folate is absorbed by a jejunal brush border enzyme, thus hypofolatemia can be used to localize a patient's disease to (at least include) the jejunum. Oral supplementation at 4 ug/kg/day is recommended to normalize documented hypofolatemia.[5] Since folate is required for nucleotide synthesis, this deficiency can also theoretically contribute to limitation on clinical recovery in patients with gastrointestinal disease.

Appetite stimulants, etc.
Achieving an adequate and consistent intake is essential, as variations in caloric load will impact glycemic control and put patients at risk of hypoglycemia. Although several drugs have been reported to support food intake in cats, most are not FDA approved for use in cats (or for this purpose in any species) and may have substantial side effects.[6]

Mirtazapine
A transdermal mirtazapine product (Mirataz®) was recently approved for the management of weight loss in cats and is likely to be a very useful option. Mirtazapine antagonizes several presynaptic receptor types within the CNS and is used in people for the treatment of depression; exactly how it increases food intake in cats is unclear, but it is likely to be via enhanced serotonin release.[7] The therapeutic window for this drug is narrow, and overdose can result in vocalization and restlessness. The recommended dose is 2 mg/cat q24h; this should be decreased to the lowest necessary dose and may be effective in some cats when administered q48h.

Capromorelin
An oral ghrelin receptor agonist (Entyce®) was FDA approved for use in dogs almost two years ago; a feline formulation is apparently under development. This drug works directly on the hypothalamic appetite center to trigger intake; it also promotes growth hormone release from the pituitary.[8] Anecdotal reports regarding the use of the canine product in cats suggest that palatability is a substantial issue.

Feeding tubes
If hyporexia is part of the manifestation of IBD, it is prudent to place an esophagostomy tube when/if the cat is anesthetized for GI biopsies. This allows the feeding of appropriate amounts of suitable food, as well as the provision of any necessary medications and supplemental hydration.

Antiemetics, acid inhibitors, etc.
Maropitant
It is unclear if 'nausea' impacts food intake in cats with IBD, but many clinicians feel that low-grade activation of the vomit center may result in hyporexia without overt vomition. Maropitant, an NK-1 antagonist, is generally well tolerated and may be helpful in cats with a variable food intake as well as true vomiting. Although it is not licensed for long term oral use in cats, many of us routinely use a 4 mg/cat q24h dose for prolonged periods.

Gastric acid inhibitors
There is little evidence to support the use of gastric acid suppressants such proton pump inhibitors (e.g., omeprazole) or H2-blockers (e.g., famotidine) in cats with IBD, unless gastric erosions or ulcers are noted during endoscopy. These drugs may impact the GI microbiome and alter the absorption of other medications and should not be used unless specifically warranted.[9]

Immunomodulators
In cats with idiopathic IBD, some form of medical immunomodulation will be necessary to improve GI tract function and mitigate clinical signs. Although these drugs may impact insulin sensitivity and increase requirements, these concerns should not prevent their judicious use.

Glucocorticoids
Oral prednisolone is the mainstay of treatment in cats with idiopathic IBD; a suitable starting dose is 1 mg/kg PO q12h. Prednisolone will predictably impact insulin sensitivity, so doses will likely need to be increased. When a suitable clinical response is achieved (likely after 3-4 weeks), the prednisone should be gradually tapered to the lowest effective dose. Complete withdrawal of prednisolone is unlikely unless an additional immunomodulator is introduced to take its place. It is often better to decrease dose amount rather than frequency during the taper, so that insulin needs can be more readily predicted. Short acting oral glucocorticoids are highly preferable to long acting depot formulations, as it is hard to predict when those will wear off and insulin requirements will go back to baseline.

Cyclosporine
This drug is routinely used for IBD in dogs, but there is limited information about its role in feline IBD.[10] It seems reasonable however to assume that it would have a positive effect in cats, and many clinicians have used it for this purpose in those that relapse as glucocorticoids are tapered. Although it has an advantage over chlorambucil in that it is not myelosuppressive, cyclosporine has been shown in other species to have substantial effects on both β cell function and insulin sensitivity. “Post-transplantation DM” is a well-recognized syndrome in people and is significantly more likely in patients receiving anti-rejection drugs in the cyclosporine family[11]. For this reason, it may not be a wise Plan B in cats that need long-term control of their IBD.

Chlorambucil
This alkylating agent and is used routinely for cats with both IBD and small cell lymphoma.[12] Its primary side effect is myelosuppression, but at standard doses (2 mg/cat q48-72h) this is generally mild and reversible. Some clinicians prefer to give 20 mg/m^2 every 14 days, but this may be more likely to cause GI upset. Because it does not appear to impact insulin sensitivity, this drug may be the most suitable choice for cats needing long term treatment of their IBD.

Glycemic control
Current recommendations regarding the management of diabetic cats focus on the mitigation of clinical signs, the avoidance of hypoglycemia and the prevention of complications such as diabetic ketoacidosis.[3] Although diabetic remission may be an appropriate goal for some new diabetics, it is highly unlikely in a cat with IBD will become insulin independent. With this in mind, it is both unnecessary and unrealistic to try to achieve euglycemia in patients with concurrent IBD, and the goal should simply be to avoid hypoglycemia and support an acceptable body condition score. It takes much less insulin to prevent ketosis than to achieve euglycemia, so BGs in the 300 mg/dL (16 mmol/L) range are not a cause for concern in the short-term.

At-home monitoring
Some owners may be able and willing to perform periodic blood glucose curves at home, using a handheld glucometer such as the AlphaTrak®. If the cat’s food intake is variable, then spot-checks before insulin administration can be very useful, so that the dose can be appropriately reduced if necessary.

Continuous interstitial glucose monitoring
In the last year or so, many clinicians have trialed interstitial glucose monitors in both feline and canine patients. The FreeStyle Libre® device appears to provide useful information in the majority of patients and is inexpensive and well tolerated. In ten dogs with DM, results were found to correlate well with plasma glucose measurements, but similar work has not been reported in cats.[13] This device does not require calibration, can be read with an app on many cell phones, and lasts 14 days. As long as the sensor is scanned at least every 8 hours, a complete record of glycemic events can be created, permitting the identification of unobserved periods of hypoglycemia.

Serum fructosamine concentrations
Measurement of glycated serum proteins (i.e., the fructosamines) provides a 7 day ‘look-back’ at BG levels. However, periods of hypoglycemia can be missed as the value provided is essentially an average. In addition,

diseases such at IBD that may shorten the half-life of albumin (secondary to loss across the GI tract) will depress fructosamine levels and limit the usefulness of this monitoring tool.

Adjusting insulin doses
As a general rule, an insulin dose should be decreased by 25% if a patient becomes hypoglycemic (BG <70 mg/dL / 4 mmol/L) and increased by 10% in the face of persistent hyperglycemia. However, the tiny doses used in cats make small dose adjustments essentially impossible, so 0.5U increments are required. Using an insulin pen increases accuracy when doses are small; if syringes are used, they should be small volume (e.g., a 0.3 mL U100 syringe). Clients should be given clear instructions about dose adjustments and cautioned against rapid increases in cats taking long-acting products such as insulin glargine (allow 3 days after a dose increase to assess the full effect).

Summary
Cats with DM and IBD present some unique challenges. Management strategies must focus on maintaining a good quality of life for both the cat and the owner. It may be necessary in the short term to sacrifice glycemic control for effective management of the GI disease, and concerns about dysregulating the DM should not hinder appropriate treatment of IBD.

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Work Life Balance & Making Time for Yourself

Melissa Tompkins, BS, CVPM

Introduction
This presentation is designed to help the overworked manager or doctor learn how to set aside time for themselves. We will discuss the challenges that we face, the reasons why we don't make time for ourselves, and how we can accomplish the vision of living a fuller, balanced, life.

What does your workday look like?
Do you stay 30 minutes, 60 minutes, or even longer after your shift is over on a regular basis to help your team? Do you regularly take work home with you or take endless phone calls when you are off because your team needs your help? Do you regularly eat your lunch at your desk? Do you feel guilty when you leave for the day when your team is still there?

If you said yes to any of these things, you may have work-life-balance problem. Many managers and doctors work long days, well beyond the time they are scheduled to be off. Many of us are very dedicated to our team and our jobs, and it can affect our ability to have a balanced life both inside & outside of work.

When was the last time you took a vacation?
If you haven't taken a vacation in a while you may have a work-life-balance problem. It is proven that people need a break from their daily life stressors. If these daily life stressors come in the form of work, then a vacation is necessity. Consider taking some time off, even if it is only a few days in order to re-charge and rejuvenate.

Many of us do not take vacations because we feel that we must be there to take care of our team. In realty in order to be our best, we "must" take care of ourselves first.

Why is it so hard for us to take time for ourselves?
There are many reasons why we take care of our hospitals and our employees before we really focus on the time for ourselves and our personal and professional needs.

We are very devoted and committed to our practices. Many times, we put our tasks aside so that we can help our team get their tasks done. While this can be helpful in the short term, this can be devastating in the long run to both you and your hospital. By delaying your tasks, you either must stay later to finish them, or put them off to a later date. Sometimes, we never go back to finish them delaying the completion completely. We need to focus on "working on the business, not just working in the business"[1]

Sometimes, we do not leave on time or take a break because we want to show our employees that we are willing to work just as hard, if not harder than them. While this is a good mentality to have, it is not always a good management skill if we burn ourselves out in the process or if we are constantly doing their work for them. The best way to show your employees that you work hard is by performing the managerial duties that are essential to have a "well managed practice." Things like handling the finances, coaching, training, performing regular reviews, and holding everyone accountable to the same rules, are just a few examples of what a manager of well managed practice is going to focus on.

There are times when we care about our teams so much that we focus on protecting them, instead of asking them to handle their own problems. An example of this is when someone calls in sick, and instead of reorganizing our team schedule for the day, we just fill in for that person. If this happens occasionally this is not a big deal, but when this happens frequently, then you need to figure out a different solution. It is important that as a leader in the hospital that you empower your team to make decisions and encourage them to be part of the solutions. This way you are not enabling them to put their responsibilities on you, instead of holding themselves accountable.

Sometimes we are so devoted to helping our practice owners that we overload ourselves with work. We take on every project, we don't take vacations, and we always say "yes" to requests for help. This is ineffective and will lead to burn out. Sometimes, we need to learn how to say no and we also need to learn how to delegate.

How Can We Change This?
For many of us, these behaviors are a habit and they will need to be broken. Of course, this is easier said than done. As psychologist Timothy Pychyl explains, they're two sides of the same coin: "Breaking a habit really means

establishing a new habit, a new pre-potent response. The old habit or pattern of responding is still there (a pattern of neuron responses in the brain), but it is less dominant (less potent)." "It's much easier to start doing something new than to stop doing something habitual without a replacement behavior," says neuroscientist Elliot Berkman.[2]

First, we need to figure out what prevents us from leaving work every day. If it is because you are not finishing your tasks on time, then you need to look at where you spend your time. Start tracking your work daily, literally write down everything you do in a day. For example, use a daily schedule and write from 9:00 am to 10:00 am you did payroll, from 10:00 to 10:30 you met with an employee to discuss their schedule, 10:30-10:45 you handled a client complaint. After keeping a daily schedule for about two weeks, it becomes very easy to see where your time is being spent. Once you know where time is being spent, then you need to look at ways to make it more efficient.

If you feel guilty, therefore not leaving work on time, not taking a vacation, or being constantly available to your team or owner then you need to focus on your self-care.

Self-Care

Self-care is all about taking care of one's self. A definition of self-care is "the practice of taking an active role in protecting one's own well-being and happiness, in particular during periods of stress." It is so important to take care of your own needs because how can you expect to be able to take care of others if you are not taking care of yourself?

What does self-care look like? Self-care looks different for everyone. The important thing is that you are taking time for yourself to do something that makes you happy.

Common self-care tips; get regular exercise, get enough sleep, un-plug from the outside world (especially your phone & email), meditate, eat a balanced diet & drink lot of water. Do something fun! Go outside and take a walk or ride a bicycle. Spend time with family & friends or read a book.

Figure out what you enjoy doing and what gives you peace and makes you happy. Sometimes we get so wrapped up in our work lives that we forget how to make ourselves happy.

Sometimes when you start to take care of yourself others will criticize you. Especially if they are used to you taking care of everything. Talk to your team, explain that you are setting boundaries and give them the tools they need to do their job without asking you first.

Make a decision to focus on self-care and stick to it!

Conclusion

Practicing self-care requires patience and practice. Remember, it takes time to make something a habit so to be good at self-care you will need to practice, practice, practice.

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What Do You Do When a Client Says No?

Melissa Tompkins, BS, CVPM

Introduction
Clients commonly say no to the recommendations that we make for their cat's health and wellbeing. We need to give our team the communication tools to encourage the client to say "yes" rather than automatically saying "no" when we make recommendations.

Who are they saying no to?
Almost all members of our team are responsible for conveying information to our clients, so potentially most of the team is involved in the recommendation process. Initially, the receptionists make the first contact with the client when they call to schedule the appointment and ask questions about our services. We need to make sure that our receptionists understand our services and the general recommendations that the doctor wants to make. We promote things like kitten packages, senior wellness plans, and even vaccine protocols that receptionists offer to the client before they even come in for their visit. Once the client comes in for their appointment the doctor, the technicians, vet assistants, and doctors' assistants also provide detailed recommendations to our clients.

What do the clients say no to?
Clients say no to things like, annual exams, recheck exams, dentistry, lab-work, parasite testing, wellness plans, medications, and a lot of other suggestions that our doctors make.

When does the client say no?
They say no over the phone when they are making the appointment. They say no while they are getting checked in for their visit, either at the front counter or to the technician who checks them into the room. Many times, they will say no when the doctor is making the recommendation during the exam. The majority of the time, when they say no, it is to the team member who is going over the treatment plan with them. They also say no when we call with updates about their hospitalized cat and ask for additional treatment.

Why do they say no?
There are many reasons that clients say no to our recommendations. One of the common ones is that they do not think their cat needs the service we are recommending. They don't think there is anything wrong with their cat therefore they do not want to spend the money. They also can be concerned that if we do find something wrong with their cat, that they will not be able to afford the treatment. Other times they feel that it is too expensive, and they do not value the recommendation or the service. Occasionally they say no at first because they are in denial and need more time to think about it. Sometimes, we also have not made their basic needs.

Maslow's Hierarchy of Needs
Abraham Maslow propose in his 1943 paper "A Theory of Human Motivation" in *Psychological Review* that people are motivated to achieve certain needs and that some needs are more important than others. He created the hierarchy of needs in a five-stage model including physiological needs, safety needs, love & belonginess needs, esteem needs, & self-actualization needs. Our most basic need is for physical survival, and this will be the first thing that motivates our behavior. Once that level is fulfilled the next level up is what motivates us, and so on[1]. Our hospitals can influence the first four stages making either easier, or more difficult for owners to agree to our recommendations.

Using "Maslow's Hierarchy of Needs" we can provide better care and communication with our clients. By looking at their physiological needs such as the need for air, food, drink, & shelter we can help fulfill that basic level. If these needs are not satisfied, the human body cannot function optimally. Maslow considered physiological needs the most important as all the other needs become secondary until these needs are met [1] This shows that clients are likely to reject our recommendations if their basic needs have not been met. Therefore, it is a good idea to have a snack bar in your lobby. If a client must wait longer than expected, then you should allow them to step out and get something to eat or drink so that they are not left being hungry or thirsty.

The next level of "Maslow's Hierarchy of Needs" is their safety needs. Clients need to feel comfortable and secure while they are at the hospital. In our hospitals this comfort would also extend to their cat as well. If a client doesn't feel that their cat is comfortable then it might be harder for them to believe in the doctor's recommendations. We need to realize that it they do not feel safe or comfortable that it can cause stress and anxiety. This means we need to keep our hospital temperature comfortable and not too hot or cold. We also need to create a calm place for both

the client and their cat to wait both before and after their appointment. If they feel safe & secure, the client will be more relaxed allowing them to evaluate their options more objectively.

Clients also need to be able to trust us. We need to help them fulfill their "love and belonginess needs" by creating a trusting relationship with them. This trust must be created by the entire team and not just one person. The client must believe that the doctor, the receptionists, the technicians, and assistants will provide good care for their cat. They must believe that we care about them as well. This trust is built through genuine and clear communication, by being empathetic and caring to their needs and making sure they fully understand what is happening. If we do not show clients these things it is very easy for them to feel isolated and alone. Remember, most of the time clients are worried about their cat and we need to provide them with reassurance and faith that we will be able to help them.

Clients also have their own esteem needs. Many clients will need positive feedback to help enhance their self-esteem. This can be done by complimenting their cat's weight loss, or by reassuring them that they did a good job by bringing the cat in when it was sick. We tend to not recognize that the client did a good thing by bringing the cat in after not eating for 3 days because we feel that they should have come in sooner. If we acknowledge the things that the client has done for their cat, this allows them to feel that you believe in them and they will trust your decisions more.

Training

Sometimes, even though we might do everything to help fulfill clients needs, build trust, and communicate with them, they still do not accept our recommendations. We need to train the team on what to do next.

There are quite a few training tools that are available for us to use. Animal Care Technologies http://home.4act.com/ has a very comprehensive training program designed for a variety of positions and experience. Dove Lewis also has a training program created for all positions in the hospital https://www.atdove.org/. There are other training programs available such as Communication Solutions https://shop.csvets.com/ and Veterinary Management Consultants https://www.vmc-inc.com/ that can also help train your team learn better ways to communicate.

In Hospital Training

Creating a written script for your team members to follow is the best way to make sure that you are all giving clients the same message.

Clients say no to many different things, so creating a specific script for each rebuttal helps your team members be better prepared to respond to your client's concerns. A few reasons clients give us for saying no to our recommendations; "my cat doesn't need it", "it's too expensive", "my cat is getting old", "my cat doesn't need a dental."

"My Cat Doesn't Need It"

Doctors recommend physical exams, lab-work, radiology and other diagnostic testing that clients decline. Some examples of scripted responses that we can say are "doctors can find things on physical exams that your cat is not yet showing symptoms of." "Cats are very adept at hiding sickness because it is inn their instinct not to show weakness in the wild. So even though your cat appears healthy there can be something going on internally that you cannot see." When recommending lab-work a good response is "our doctors can only see so much on physical exam and the lab-work is like a window into the kitty's body to get more information."

"It's too expensive "

This response can be difficult because sometimes they really cannot afford the treatment, but other times it is because they do not see the value in the recommendation. When a team member goes over the cost of the recommended treatments, they need to make sure that the client understands the value of the treatment. Team members should always review the detailed information with the client before giving them the cost. They should be able to answer the client's questions before going over the numbers. Many times, clients need to hear the information multiple times before they feel comfortable with the recommendation. They might appreciate handouts or brochures, or even videos that provide additional information about a product or service. Team members should be able to access this information easily to help clients make educated decisions.

When clients do have legitimate financial concerns, all team members must be trained on the financing options that the hospital has available for their clients. Some of these options include; CareCredit, Scratch Pay, Wells Fargo Financial, Sunbit, Pay Pal, and hospital payment plans. Managers and practice owners should make sure that every team member that goes over the treatment plans knows exactly what options the hospital has and how to use them.

My Cat is Getting Old
Some clients feel that when their cat gets old, they become concerned with spending the money on care. We need to reassure them that if we find a problem and get started on the treatment early that it could give their cat a longer, fuller life. It is important that team members can convey this information in a compassionate way. By also reminding that if treatment or diagnostics are delayed, it could make the treatment more complicated or even more expensive.

Sometimes clients are also worried that if the doctor finds something wrong with their cat that they will not be able to afford treatment. The team needs to remind them that sometimes the results come back positive and the cat does not require any treatment, but that it would give the client peace of mind. If a hospital recommends senior plans this is a good way to help encourage clients to do them.

My Cat doesn't Need a Dental
Dentals can be expensive for clients and sometimes they just do not think they are necessary. In the exam room doctors should show the client the cat's teeth if they are going to make a recommendation to clean them. They need to explain the grade of dental disease the cat has and make sure to convey that the cat could be in pain. Clients do not want their cats to be in pain and are more likely to take care of the problem when they know that.

Team members should also be trained to communicate this information with clients and recognize when they should offer the hospital's financial options to the client. By also advising them about other heath issues that can be cause by dental disease this can help clients understand how better dental care impacts the overall health of the cat. A lot of clients are fearful of doing dentals because they have their own fear of the dentist. By explaining the teeth cleaning process to the client, it can help them feel more comfortable about the process.

Conclusion
Each hospital should discuss what clients are saying "no" to in their hospital and find a consistent and specific way they can communicate to the clients about their resistance. The team needs learn how to build trust, create a relationship, and be knowledgeable about the options available to clients. Each team member be trained on how to respond appropriately when clients say "no" and communicate effectively when making recommendations.

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Impact of Environmental Design & Choices on the Cat

Ragen McGowan, PhD

Introduction

Our understanding of the emotional lives and experiences of pets is quickly growing. As a result, there has been a call to rethink veterinary clinic design, and ways of working, taking into account the pet's point of view. The goal is to promote wellbeing by creating clinic environments that are emotionally supportive to pets. Without careful consideration, trips to the veterinary clinic can be as emotionally draining for the pet owner as for the pets themselves. For cats in particular, owners are faced with several hurdles to achieve a successful visit starting with the challenge of transporting their cat to the clinic safely, followed by worry of how their cat will react once at the clinic and often how their cat is handled during veterinary procedures.[1] Some cat owners will forgo trips to see their veterinarian or wait until their cat's symptoms are severe before taking the step to make an appointment. In either case, a cat's welfare could be compromised if that cat is not receiving the medical care he or she needs simply because his or her owner is worried about what an appointment will entail. To improve this, we must rethink the veterinary clinic, and its ways of working, by stepping back to consider the entire experience from the cat's perspective; to create an environment that provides the best care for cats while minimizing stress for the cat, staff and owners alike.

What is the harm of a little stress at the vet?

For cats, sudden movements, unfamiliar noises, large swings in ambient temperature, unfamiliar objects and the approach of strangers can all be stressors. None of which would be out of the ordinary for a cat to experience on a typical trip to the veterinarian. While the whole point of taking one's cat to the veterinarian is to ensure his or her health, if a cat is overly stressed during the experience he or she can actually begin to express sickness behaviors.[2] In a potential "catch 22" situation, the trip to the veterinary clinic can result in the manifestation of nonspecific clinical and behavioral signs that include such things as vomiting, diarrhea, loss of appetite, decreased water intake, lethargy, pain-like behaviors, ceasing of self-care and withdrawal from social interaction.[2,3] Thus, even a clinically healthy cat can start to show signs of sickness as a coping mechanism to the present situation.

Seemingly, cats start to exhibit sickness behaviors in response to stress as their bodies shift into a recuperating mode, where energetically expensive activities are suppressed in favor of activities that contribute to recovery. This behavioral reaction is likely triggered by the release of glucocorticoids and subsequent activation of the sympathetic and immune systems.[4] Sickness behaviors have been documented in many species in response to aversive events.[2,4] Thus, it is feasible that simply the stress of coming to a veterinary clinic could elicit symptoms in their own right, making it difficult to diagnose actual illness in cats. While potentially an issue during a typical visit, the concern is greater if hospitalization is required, with previous research suggesting that over 80% of cats exhibit some form of sickness behavior during the first 24-hours after entering a clinical setting.[5]

Not only can stress manifest into sickness behaviors, but it can also trigger rapid changes in a cat's physiological state making abnormalities in diagnostic tests difficult to interpret.[1] The typical physiological responses of cats to a stressful situation can include, just to mention a few, changes in cardiac activity, respiration rate and body temperature, increased circulating cortisol, and increased urinary cortisol:creatinine ratios[3], many of which can impact the interpretation of routine health screenings. Abnormal test values resulting from stress can potentially lead to unnecessary or repeat diagnostics and perhaps even inappropriate short-term treatment plans.[1] There is also evidence to suggest that, for cats, emotional stress has the potential to reactivate subclinical conditions[6] and inhibit the production of mucosal antibodies[7], resulting in increased susceptibility to upper respiratory infections.[8,9] In fact, in as little as four days after transferring to a new environment, cats can go from zero to severe upper respiratory symptoms.[9]

In addition to compromising animal welfare, stressed cats with increased incidence of sickness behavior can make the job of the veterinary staff more difficult. If a cat is being held for observation and refuses to eat or drink the staff may be required to handle the cat more in attempts to entice consumption, hand feed, tube feed or provide subcutaneous fluids. If the same cat ceases to eliminate, the staff may need to resort to cystocentesis, suppositories or direct fecal loops in order to collect necessary samples for diagnostics.[1] These added procedures could lead an already frightened cat to resort to aggression if he or she feels unable to escape or control the situation. This cycle creates dangers for the cat and the care staff, potentially limiting the care they are able to provide for the cat.[10] Thus, creating a clinic atmosphere and ways of working which minimize the stress for the cat can go a long way towards providing opportunities for better care.

So what can we do to minimize stress in the veterinary clinic?

When asked to think about potential stressors in a cat's environment most people jump immediately to aspects of the micro-environment (e.g., carrier, enclosure, exam table), however it is also important to consider changes in the macro-environment (e.g., noise, lights, odors, general routine). These environmental factors will affect cats differently depending on whether they are long term (e.g. relating to an enclosure where a cat is housed) or short term (e.g., waiting room or exam room at a veterinary clinic) and whether they are able to control or move away from a factor that they find aversive. There is evidence to support that sometimes the effect of the room is greater than the effect of the enclosure.[5]

Quality of space is more important than quantity. Several studies in the literature provide evidence that simply increasing enclosure size alone does not seem to have a positive impact on behavior. [5,11,12] Therefore, enclosure size may be of lesser importance to the cat, particularly in the first few days of confinement, than an enriched space. When confined to an enclosure, cats should be provided with enough space to allow them to express normal behavior and allow for clear separation of eating from eliminating and sleeping. This can include utilization of both horizontal and vertical spaces.

It is important to remember that it is not necessary to replicate a natural environment for cats in an unnatural setting. Rather, it is imperative to provide the cat with the opportunity to interact more with his or her surroundings, if he or she wishes to, and to perform behaviors that are important for that individual.[13] The goal is to give cats a sense of some sort of control and the ability to cope with a potentially stressful situation.

Visual Considerations: Do you see what I see?

Animals perceive the world differently than humans so visual attributes that go unnoticed by most humans can actually be quite impactful to most animals. For example, when considering lighting, whether it is natural, fluorescent, incandescent or LED, the intensity and flicker frequencies can all affect animal welfare.[14] Of particular importance for cats is that they are able to visualize the ultraviolet end of the light spectrum. Their lenses transmit a significant amount of UVA, only slightly less than some rodents, suggesting that they are UV-sensitive.[15] In practice, this means that bright white objects will fluoresce for cats, similar to how humans perceive white objects under a black light. In our attempts to make things look crisp, clean, and sterile in the case of a clinical environment, humans incorporate optical brighteners into many products. Imagine now from the cat's perspective…how startled would you be if someone wearing a glowing lab coat was to walk into an already unfamiliar room and approach you? What about someone attempting to wrap you up in a glowing towel? Cats are capable of distinguishing colors even under low light or different colors of illumination[16] and pastel colors (that do not fluoresce) are more calming (or at least less stimulating) for cats. Pale blue, green, gray or purple are good choices for veterinary staff to wear and even for blankets, towels, bedding or other materials with which cats will come into contact. Extending a similar pastel color scheme beyond the micro-environment and into the macro-environment with wall and floor colors can also aid in creating a more calm atmosphere.

In addition to color, it is also important to consider carefully the texture and sheen of surfaces with which the cat will come into contact. Not only do slick surfaces pose an issue for cats to find secure footing, the added visual stimulation of reflective surfaces can cause fear or agitation. Enclosures and exam tables with low-gloss finishes such as matte stainless steel, high-pressure laminate or pastel colored resin products can help a cat feel more secure.[17] Aside from the visual aspects of surfaces, texture can be just as important as cat's paws are highly sensitive and their paw pads contain large concentrations of nerve receptors to help test for safety/stability and temperature.[18] Cats feel the texture of surfaces, vibrations, and gravitational pull through their paws, helping them both detect prey and maintain balance. Accordingly, materials that limit both reflection and vibration and maintain comfortable temperatures (with a cat preference towards warmer) are most appropriate for a clinic environment to minimize the stress of feline patients.

The visual system of the cat is highly tuned to detect movement, as is necessary to facilitate a successful hunt. As a result, rapid movements can elicit a heightened state of arousal transitioning cats from a calm state to a playful or predatory state rather quickly. Careful consideration should be made when working around cats (especially in an unfamiliar setting) to favor slow methodical movement over rapid or unexpected movement. Keep in mind that the visual acuity of cats differs from humans. The details that humans can see from 30 to 60 meters away are only visible to cats once they are six meters away and cats have difficulty focusing on objects that are closer than 26 centimeters.[19] People or objects outside this field of vision will appear blurry to cats and this uncertainty can lead to heightened vigilance or anxiety. In considering the design of exam spaces and enclosures for cats, it is important to provide the cat with a relatively unobstructed view of the room. Traditional enclosures incorporating vertical bars restrict the view and hamper the cat's ability to survey the horizon. Switching from vertical bars to horizontal bars provides cats with a better opportunity for surveying the room. Some veterinary practices have also had success with built-in panels with ventilated Plexiglas providing wide-open views for cats.[17]

It is generally recommended that cat enclosures should be elevated at least one foot above the floor, with further recommendation for cat enclosures to be elevated to shoulder height[20] to better provide cats with the opportunity to survey their surroundings. Cats prefer to monitor their surroundings from elevated vantage points, so the provision of climbing structures, platforms, shelves or window seats[21] can increase the usable enclosure space in a manner that is meaningful to a hospitalized cat. In a home setting, cats spend more than five hours per day looking out of windows[22], suggesting a natural motivation for visual simulation. When possible it is also good to provide cats with the opportunity to view the outside or neutral indoor spaces where people are performing routine tasks. The ability to survey what is going on can help to reduce the stress of the veterinary environment. There is at least some evidence to suggest that species-specific visual stimulation (e.g., cat centric videos played on screens visible to the cats) incorporating elements of prey movement can be enriching for cats.[23] Providing opportunities for visual simulation in a clinic environment could go a long way to promoting optimal welfare states by providing elements of positive stimulation in an otherwise sterile environment.

While providing visual stimulation and the opportunity to survey the surroundings in the clinic environment is important, equally important is allowing cats the opportunity to escape this visual stimulus or to survey from a concealed location. For cats, hiding is an adaptive response to threat of predation and they are motivated to perform this behavior in threatening environments, such as veterinary clinics. There is evidence to suggest that barring attempts to hide can significantly increase a cat's overall stress.[3,21] Provision of hiding boxes to cats when first introduced to a novel environment can reduce the expression of stress behaviors, rapidly reduce physiological indicators of stress (e.g., heart and respiration rate) and help cats to adjust more quickly to their new surroundings,[24] even in a short-term inpatient setting.[25] In fact, when offered the choice of multiple enrichments catered to different motivational systems, cats will allocate the most time towards boxes that provide a hiding opportunity.[26] Admittedly, this presents some logistical issues in a clinic environment where medical staff must be able to easily monitor the cats in their care. Despite popular perception that if cats are provided with hides, they will always be hiding, there is evidence to the contrary. Shelter cats provided with Hide, Perch & Go boxes come to the front of their enclosures to approach unfamiliar people more, retreat less and are seen sleeping restfully more often than cats who do not have access to these boxes.[27] In addition, cats who have the choice to hide often show less vigilance behaviors and less anxious behavior than cats without this option.[27] Thus, simply having the choice to hide/perch seemingly reduces the stress levels of cats. For the more fearful cat, who does choose to reside within a hide long-term, opportunities for cameras or other technology for monitoring cats may help to reach a happy medium between both cat and staff needs.

Olfactory Considerations: What's in a smell?

Cats are more sensitive to subtle chemical changes in their environment and utilize olfactory cues to a greater degree than humans do, so aversive odors can be an additional source of stress in an unfamiliar environment. In a veterinary clinic, cats can encounter what, from a cat's perspective, might be particularly objectionable odors. This may include the smell of dogs or other animals (if a mixed species practice), unfamiliar conspecifics, air fresheners (appealing in waiting rooms), alcohol (from wipes or hand sanitizers), cigarettes (odor from employee uniforms), cleaning chemicals (including laundry detergent) or heavy perfumes. Careful consideration should be made to minimize these environmental odors in areas of the clinic to which cats will be exposed.

Cats communicate through olfaction using saliva, urine, feces and scent marking (rubbing and scratching). While cats seem to find comfort in their own scent or that of close conspecifics, other patients can leave behind messages that convey a sense of threat. It is important to have proper cleaning procedures to minimize carryover between patients. Soft materials such as staff uniforms, lab coats, blankets or towels utilized in the clinic environment may carry pheromones (see below), fur, blood or other residues from patients. Similar residues may linger on the hard surfaces of enclosures or exam tables as well if not properly cleaned between patients. Though cleaning between patients is critical, it is also important to consider that for hospitalized patients, a thorough cleaning may remove much of the cat's own scent and sense of security. For these patients, spot cleaning of waste materials or bodily fluids may be sufficient so as to maintain the cat's own scent in the environment.

Although not without some confounds, there are several studies in the scientific literature that point to the potential for feline facial pheromones/pheromone analogs to promote affiliative behavior in cats. Pheromones are chemical compounds that have evolved for communication within species and they play an important role in many contexts. The response to pheromones is such that when one individual emits a pheromone, another typically responds in a stereotyped manner. Cats process pheromones through the flehmen response where molecules are drawn into the innervated vomeronasal organ, linking directly into the limbic system (part of the brain that regulates emotions, mood and memory). Upon pheromone detection, cats show activity in the limbic system and the hypothalamus manifesting into changes in physiology and behavior. Depending on the context and pheromone employed, utilization of pheromone sprays or diffusers in the clinic setting may reduce the probability of aggressive behavior[28,29] and make

social interactions easier.[30] In addition, there is a potential for pheromone treatment to help reduce the expression of anxious behavior,[31] and the level of restraint necessary to perform clinical examinations,[32] even for cats with known fears of veterinary professionals.[33]

In addition to the use of pheromones to modulate stress and behavior in the clinic setting, there is also potential for the use of scents as olfactory enrichment. The literature reports mixed results when it comes to using scents as olfactory enrichment for domestic cats with some scents leading to reduced activity and others promoting play.[34] Only scents with documented evidence of the effect should be employed in a clinical setting, as the behavioral reaction is not always intuitive; for example, both catnip and prey scent leading to reduced activity, more resting and more sleeping.[34]

Auditory Considerations: What's that noise?

The audible frequency range and decibel sensitivity for cats exceeds that of humans, so what we deem a relatively quiet space could actually be quite loud for our feline companions. While natural sound levels for the savannah and forest environments where cats evolved range between 20-40 dB,[14] noise levels in shelter, laboratory or clinical settings can exceed 100 dB.[35] Most humans do not hear frequencies above 23 kHz, whereas the upper limits for cats may exceed 70 kHz.[36] Many electronic devices (e.g., clippers, medical equipment, cleaning devices) as well as aspects of the ambient environment (e.g., fans, lights for HVAC systems) emit ultrasonic noise that may be innocuous to humans but aversive to cats. Keen observation of a cat's reaction when specific equipment is switched on/off (e.g. ear flicking) can provide insight into what they may find aversive or overstimulating. While our understanding of ultrasonic disturbances for cats is in early stages, much work supports the notion that audible loud noise (e.g., dogs barking[37]) increase the stress levels of cats.

A handful of studies in the literature provide evidence towards the positive impact of playing species-specific music to promote calm behavior in pets. A market for creating species-specific music was spurred by the idea that the development of the emotional centers in the brain occur shortly after birth, during the nursing stage for most mammals, so incorporation of similar sounds into music has the potential to elicit emotional reactions. For cats specifically, because purring and suckling sounds are common in this developmental window, music incorporating tempos and frequencies that mimic these cat-specific sounds may be soothing.[38] Cats in home show a preference for cat-centric music that incorporates both affiliative cat vocalizations and preferred tempos over classical music.[39] In a veterinary setting, playing cat-specific music during clinic visits decreases behavioral signs of stress and seemingly makes cats easier to handle during physical exams.[40] A more relaxed, more easily handled cat can make collection of vitals and physical exams go much more smoothly. Thus, it has been suggested that incorporating cat-specific music into veterinary clinics may directly improve cat welfare as well as owner perception of the veterinary team (if the cat is more relaxed as easier to handle) as well as allow for better diagnostics (easier to assess and collect samples from a more relaxed cat).[40]

Social Considerations: Creating and promoting that bond

One of the most powerful factors in the promotion of positive affective states for our companion animals is the human-animal bond. In a veterinary setting it is critical not only to utilize the relationship between cats and their owners to aid in treatment and recovery (a good clinic design will incorporate space for this), but also to foster the relationship between pets and the veterinary care staff. For cats, potentially the most stressful part of visiting a veterinary clinic is forced interaction with unfamiliar people. Many cats react fearfully towards strangers and may even perceive encounters with strangers as predatory.[41] From a cat's perspective, a visit to the veterinary clinic includes meeting strangers who intrude into their territory, bend over them, examine them, poke and prod them and potentially separate them from their bonded human companion for short periods. This can be quite stressful for a cat, leading to a fearful response. In turn, fearful responses of cats can lead to negative attitudes of caretakers, increasing the likelihood of poor interactions perpetuating. The key is to change the cat's perception of care staff members from strangers to friends. A change that can occur rather rapidly through positive, predictable interaction.

Before reaching the exam room, there are steps owners can take to help minimize the stress of the cat upon arrival at the clinic and to ensure the best possible outcome of the visit. One such step is carrier training. Not only does training at home provide opportunities for increasing the cat-owner bond, but carrier trained cats show a significant reduction in stress related behaviors upon arrival at the veterinary clinic.[42] Cat owners should also be encouraged to practice car trips with their cats in carriers and promote positive associations with carriers by rewarding cats with praise, treats and toys for both entering and exiting the carrier. The benefit for veterinary care staff will be cats that arrive at the clinic in better mood states and cats who willingly enter and exit the carrier leading to significant reductions in examination time.[42]

Unavoidably, most routine veterinary procedures require some form of restraint for the patient and restraint can be an immense source of stress for cats. Many cats respond with fear and/or aggression when handled by unfamiliar

people. In the veterinary setting, an extreme response can result in an incomplete examination, with the potential for inadequate or inaccurate diagnosis and treatment.[43] Furthermore, cat owners are sensitive to the way their cats are handled during veterinary procedures and if their cat protests too much during handling this can lead to distrust of the veterinary staff. There is now evidence to support the notion that passive low stress restraint is more effective than full body restraint for many veterinary procedures. On average, it takes veterinary care staff longer to place cats into a full body restraint compared to passive restraint.[43] Once in restraint, the odds of a cat struggling are higher when employing a full body restraint. Cats also show higher respiration rates and increased behavioral indicators of stress such as lip licking and flattened ears during full body restraint as compared to passive restraint.[43] Perhaps most telling of the emotional state of the cat, passively restrained cats are more likely to remain on the exam table following the procedure than fully restrained cats who are more likely to attempt to flee the situation.

Interestingly, in a direct comparison between cats examined using low stress handling techniques in a clinic versus a home setting, most physiological stress markers were comparable between the two environments save for blood glucose, which was higher in the clinic environment.[44] The behavior of the cats was also comparable between the two environments except for cats being more likely to hide in the clinic environment.[44] Moreover, in both environments circulating cortisol was diminished over repeated visits[44], suggesting that the low stress handling techniques were not creating a negative association with the veterinary exams. Positive interactions, such as short periods of petting, can improve both the emotional and immune state of cats.[9] Even just performance of routine husbandry tasks such as frequent changing water and food bowls can increase the familiarity of cats with staff members and increase their willingness for contact.[45] Thus, providing clinic staff with the time and opportunity to interact with cats during routine cleaning tasks can potentially benefit the welfare of the cats.

Control and predictability of caretaker behavior are of great importance to how cats perceive veterinary staff members. Studies with numerous species have demonstrated that consistent, positive, predictable interactions by caretakers lessen the stress response of the animals in their care, improving welfare.[5,46,47,48,49,50] By stepping back and considering all aspects of the clinic environment from the cat's perspective, we can move towards environments that promote optimal states of wellbeing.

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Feline Professional Liability Risk Management

Linda Ellis, DVM

Feline practice is many things including fun, challenging, and rewarding. Like other types of veterinary practice, the not so fun part can be dealing with upset clients or clinical cases that do not turn out the way we hoped. At some point in their career, many practicing veterinarians will face a potential or actual malpractice claim or Board complaint. The AVMA PLIT provides Professional Liability for 65,000 veterinarians and on average 1 out of every 17 submit a potential or actual claim every year. There are steps that can be taken to minimize the risk of a claim, however mistakes and unfortunate events can happen. This goal for this session is to provide information on issues related to Veterinary Professional Liability (Malpractice) in feline medicine. Topics to be discussed include communication, client consent, medical errors, client injury, and record keeping. Some of the more common examples of feline professional liability claims brought against veterinarians will be discussed using actual claim examples. How to manage a complaint and the process of reporting a potential claim will also be covered.

Some of the more common reasons for malpractice and board complaints are communication problems, adverse events or unfortunate outcomes (related to an inherent risk), negligence(mistake or error), human injury(when a client is injured during the course of you treating their animal), and fee disputes/collection activity(often prompt countersuits). Communication problems can be exhibited in many different ways, from lack of communication to miscommunication. There are many people involved in communication within a veterinary practice: the veterinarians, technicians, veterinary assistants, receptionists, and clients. Being aware of the importance of communication, developing standard practices and policies, and getting training for the entire staff can help prevent a claim related to a communication breakdown.

A critical piece of communication with the client is obtaining and documenting client consent. Owner attorneys are increasingly using an allegation of lack of client consent in claims and lawsuits against veterinarians and are often successful. The veterinarian needs to discuss risks vs. benefits of a medication or procedure they are recommending and provide written information to owner when indicated or appropriate. Documentation in the medical records is important to support client consent was obtained or that appropriate recommendations were made, etc. Medical records are the veterinarian's defense if a claim is brought. Medical records that are illegible or incomplete often lead to fines if a Board complaint is made. It is important to understand that your state Veterinary Practice Act is the law and ensuring that you are in compliance can help prevent a Board action against your license.

To avoid malpractice and Board complaints, focus on practicing good medicine, good communication skills, and keeping clients out of harm's way. Good medical records are crucial to defend yourself in the event of a claim. Managing a potential claim situation may include submitting a report of claim to your liability carrier for advice on how to communicate with the client in your particular situation.

The most common feline claims seen through the PLIT program are related to common medical and surgical procedures performed in feline practice. On average 17% of the claims submitted each year involve cats. The following are examples of some of these claims:

Dental related claims:
14 year old MN DSH presented for dental cleaning and extractions. 9 extractions done- surgery and post op uneventful. Next day owner reported cat showing signs of discomfort and took to subsequent DVM who reportedly sedated and took full mouth rads. Several retained roots were removed as well as sutures from 104 extraction site to alleviate tension.

4 year old MN Siamese presented for dental surgery. Few days later skin lesion reported. Lesion progressed, thermal injury during dental procedure suspected. Referred for derm consult. Heated disc in microwave reportedly used during 2 hour surgery. Thermal burn confirmed.

7 yr. old MN DSH presented for a dental cleaning. During the procedure the dental bur slipped and caused damage to the sublingual mucosa. The cat developed a mucocele from the damage to the salivary duct.

7 year old MN DSH for dental cleaning and extractions on. Two days later cat seen for SQ emphysema- tracheal tear due to intubation during dental procedures suspected. Referred for continued care.

10 year old FS DSH for dental procedures. Syringe cap used as mouth gag. Cat blind after. Referred where retinal ischemic injury diagnosed due to use of mouth gag and maximal jaw opening during dental procedure.

Human Injury related claims:
Insured and assistant doing home euthanasia on a 16 year old MN Bengal. Owner insisted on holding cat. Cat was not showing any signs of fear or aggression. Insured advised owner when starting to give IM sedative but cat reacted and bit owner's hand. Euthanasia completed and owner advised to seek medical care which they did. Owner subsequently required hospitalization and reportedly will likely not regain full function of hand.

2 year old FS DSH presented for rabies vaccine. Tech was in room but not holding cat. Insured gave vaccine and instead of running into carrier cat turned to jump off table. Both insured and owner reached at same time to grab cat and insured still had syringe in hand - needle stuck owner in hand.

Client presented cat for lethargy and weight loss. Insured examining cat that was quiet initially then began growling. Owner began petting cat while insured listened to cat's heart. Cat suddenly turned and bit owner's finger. Owner was instructed to wash finger. Several days' later finger swollen and owner went to doctor. Client was a diabetic. Cellulitis and necrosis occurred leading to skin graft which failed. Amputation recommended but client declined and filed suit. Demand was $250,000. Settled for $187,000

Practice adopted kittens out from clinic- skin lesions /scabs attributed to flea infestation at presentation. Family contracted ringworm.

Blocked Cat claim:
A five year old indoor-outdoor blocked cat (MN DSH) was referred to 24/Hour Clinic. Primary DVM was unable to pass catheter and clinic was closing. Upon presentation the cat was 5% dehydrated, extremely lethargic and had elevated renal values. Treating DVM explained to the owner that there was a risk of urethral tear due to the long-standing nature of the block, previous attempts to unblock and that the urethra could be compromised and friable. The owner consented to treatment and the cat had an IV catheter placed and was sedated. Several attempts were made to pass the catheter while gently flushing. Some swelling of the perineum developed and urethral tear diagnosed. The owner became extremely upset and took the cat for a second opinion where the tear was confirmed and surgery done.

Drug errors and related claims:
11 month old F DSH. Tech accidentally gave injection of rimadyl.

7 yr. old NM DSH cat presented for abscess from cat fight. Cat was given the wrong dose injection of meloxicam (0.7 mls instead of .07 mls) that was drawn up by a technician. Cat was treated at ER for overdose.

7 year old DSH was prescribed oral meloxicam following FHO and developed acute renal failure. Owner alleged risks and extra label use not discussed.

Advantix accidentally dispensed for cat instead of Advantage

Cat received azathioprine instead of intended azithromycin when veterinarian inadvertently called in wrong prescription.

Ownership issues:
5 year old MN DSH presented for euthanasia. Not medical necessity so declined to euthanize. Owner then agreed to sign ownership over and cat adopted out. Owner wanted cat back shortly after and had attorney send letter.

Patient injury during exam:
7 year old FS DSH for recheck urine. Tech reported cat was being fractious and escaped in treatment area. Cat ran up on counters and through open doors into surgery and radiology. Was recovered under radiology table. No injury noted because cat placed back into carrier. Owner reported cat seen at SDVM and diagnosed with Achilles tear.

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Does Cat Friendly Practice Impact Your Team's Risk of Injury?

Scott Simpson

Introduction

Employee Safety is central to a healthy and productive veterinary practice. Scott Simpson, Risk Consultant with the AVMA PLIT, will present a high level overview of Worker's Compensation data to determine how Cat Friendly Practices are applying safe handling procedures to reduce their Worker's Compensation claims. Discussions will center on important components of a robust safety program for Cat Friendly practices, and will include information regarding OSHA safety requirements that every veterinary hospital must comply with.

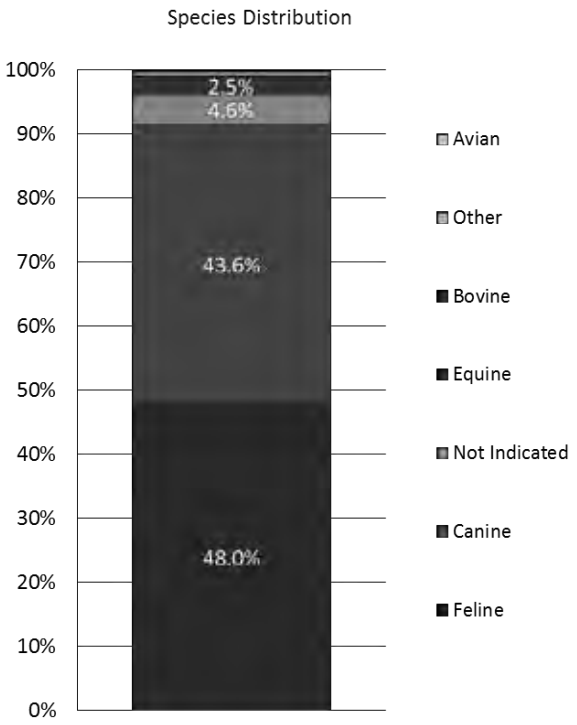
AVMA PLIT Worker's Compensation claim's data[1] is presented in these proceedings notes, and may be used as a benchmark when comparing claims data for a particular practice or group. This data will also be used to compare data points specifically to Cat Friendly Practices.

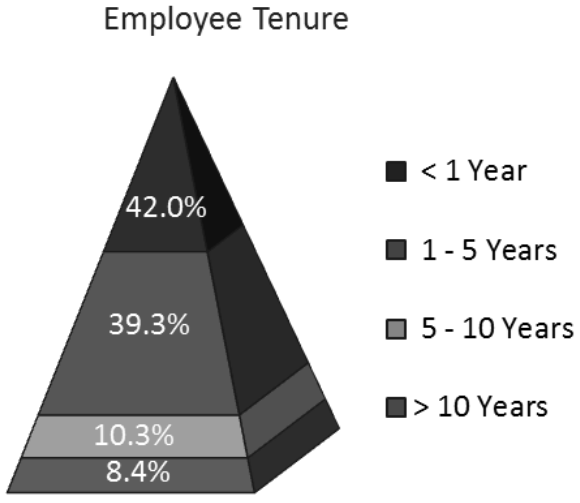
Worker's Compensation Claims

Worker's Compensation Claims are a major cost for a veterinary practice. The AVMA PLIT finds that the average cost for a single claim is over $3,200; with practices often submitting dozens of claims each year. High frequencies and severities of Worker's Compensation claims can have a negative impact on a practice's mod factor. In most states, a Worker's Compensation Modification Factor is determined by the National Council on Compensation Insurance (NCCI) to analyze the cost of losses from a practice which establishes a comparison to the rest of the industry. This modification factor directly affects how much a practices pays for Worker's Compensation insurance, and practices with a high mod factor may pay anywhere from 10% to double that of their industry peers with lower mod rates.

In relation to AAFP practices, it's important to understand how practices can directly lower their claim costs. The AVMA PLIT has found that nearly 50% of these claims that are related to contact or exposure to an 'animal attack' are due to contact with a feline patient, and these claims can be especially dangerous with a higher likelihood of infection if not treated properly.

In addition, nearly half of employees have been employed at a the practice less than a year at the time of a Worker's Compensation claim, suggesting that a younger workforce with less experience is much more likely to experience a workplace related injury. These factors will contribute to the analysis of claims related to Cat Friendly Practices.



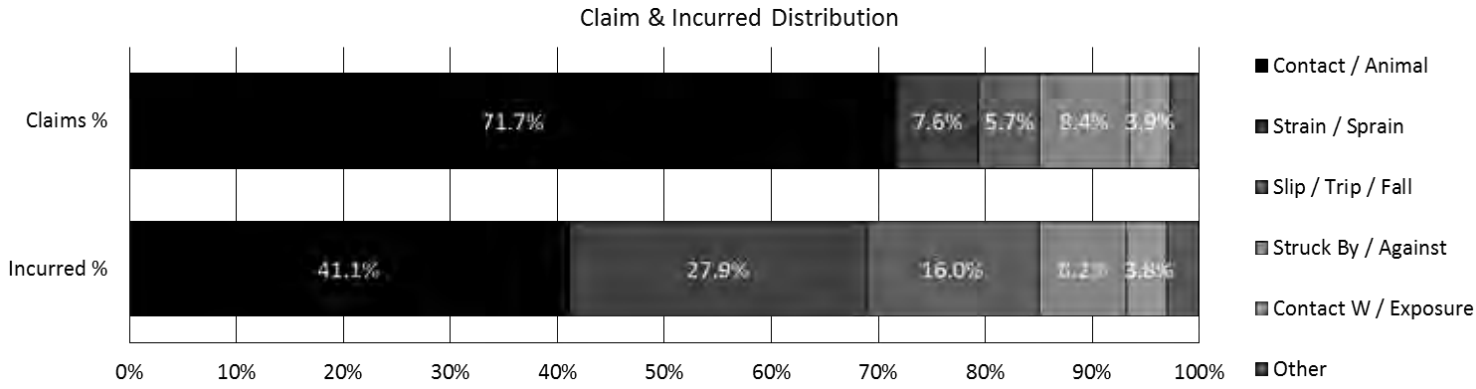


Claim Type

On average, a Worker's Compensation claim that involves contact or exposure to an animal will cost $1,600 per claim. Out of all of these claim types, an animal contact claim is easily the most prevalent, with over 7 out of 10 claims being related to an incident with an animal bite or scratch. While this may be understood for an industry that has a heavily reliance on handling unpredictable animals, much of this risk can be reduced with proper handling methods. In particular, Cat Friendly practices place a heavily emphasis on a stress free environment that should directly correlate with employee safety when conducted properly.

The averages below can be used as a benchmark when comparing claim costs for a specific injury type.

Injury Type	Average / Claim
Contact / Exposure to Animal Attack	$1,600
Strain / Sprain	$10,224
Slip / Trip / Fall	$7,861
Struck By / Against	$2,737
Contact With / Exposure To	$2,749
Caught In / Under / Between	$1,173
Cut / Puncture / Scrape	$454
Other	$14,442



Body Part Affected

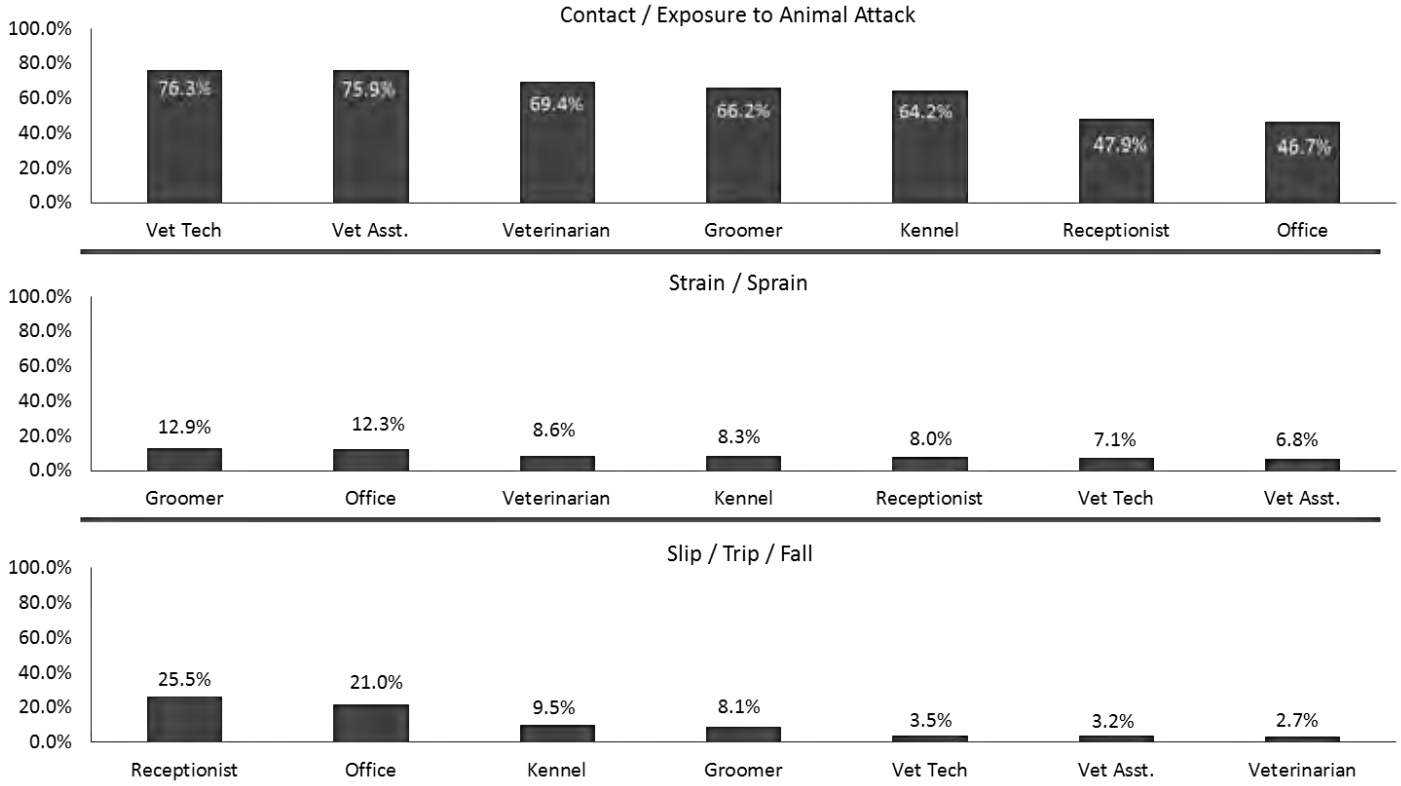
The highest total incurred cost when examining a Worker's Compensation claim in relation to the body part affected for a veterinary practice is attributed to hand and wrist injuries. It's important to note that injuries to the arm, shoulder, back and neck – while less common, typically are attributed with a larger cost and are caused due to strains and sprains received on the job.

The averages below can be used as a benchmark when comparing claim costs for a specific body region.

Body Part Affected	Average / Incurred
Hand / Wrist	$1,267
Arm / Shoulder	$4,399
Back / Neck	$9,456
Leg / Knee	$7,087
Head / Face	$2,282
Foot / Ankle	$4,894
Multiple	$4,676
Abdomen	$3,974

Claimant Occupation

Claimant Occupation is an important metric when evaluating Worker's Compensation claims. While claims regarding animal handling are generally attributed to Vet Techs/Assistants/Veterinarians, a high frequency of claims related to strains/sprains and slips/falls are attributed to non-care related employees. Associates at the front office, as well as groomers and kennel attendants are exposed to these workplace hazards as well, and it's important to remember to include all staff and employees in safety training procedures.



Risk Management Program

A Risk Management and Safety program is essential to every Cat Friendly Practice, and it's highly recommended to implement both a team safety committee and a risk management or safety leader to facilitate and lead this team.

Components to a well-rounded safety program include an understanding of OSHA Compliance, Facility Safety Guidelines, an Emergency Action Plan, a Hazard Communication Plan, and access to the necessary Personal Protective Equipment.

References

1. Worker's Compensation data for the veterinary industry comes from the AVMA PLIT and HUB International in partnership with industry specific insurance carriers. Claims data is a three year snapshot of roughly 10,000 worker's compensation claims in the veterinary industry and is meant to be a benchmark resource.

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Incorporating Feline-Friendly Techniques into Practice Management Decisions

Melissa Tompkins, BS, CVPM

Introduction

What is a Cat Friendly Practice® (CFP) and why should you become one? As many of you know, the concept for a Cat Friendly Practice® came about from the Bayer-Brakke Study in 2010 that found that even though cats made up 55% of the pet population they only represented on average about 39% our patients[1] Established by the American Association of Feline Practitioners (AAFP) and the International Society for Feline Medicine (ISFM), the Cat Friendly Practice® program is a global initiative designed to elevate care for cats by reducing the stress for the cat, caregiver, and also the entire veterinary team[2].

There is an 80% grow potential in cats[1] and by focusing on feline care we can make this a reality. In 2018 79% of CFP hospitals saw an increase in revenue[2]. Managers have an opportunity to increase their cat visits and new cat patients. By focusing on building their feline clientele and using the as the tools that AAFP has to offer they can make that happen.

Goal

The goals of becoming a CFP[2];

- To create a more calming environment for cats.
- To increase staff member's comfort in handling cats.
- To elevate your hospitals ability to provide the highest standard of feline care.
- Minimize stress during procedures of hospitalization.
- Helping improve communication with clients.
- Educate consumers about the need for routine and proper feline care – "find your hidden feline patient."

Where do you start?

The first thing to do is sit down with your practice owner and determine if becoming a CFP is right for your practice. There are 10 topic areas that you will have to focus on to become a CFP and you need to make sure that your owner is committed to doing so. Becoming a CFP and focusing on providing a more calming environment for cats is something that involves the entire team and you will need your owner's and other leaders in the hospitals support for this to be successful.

Once you have decided to become a CFP what is needed to qualify?[2]

- Go to catvets.com and start the application process
- The hospital must have an AAFP member in the practice
- Need to get the educational materials and the 10 feline care topics to self-asses your practice with standard checklist criteria
- Select a cat advocate who will be the person who reviews the checklist and implements the changes necessary to qualify
- Everyone one the team will need to be trained on feline friendly handling technique & guidelines.
- Photos of the hospital will need to be submitted to AAFP for specific things on the checklist

There are two different levels that a hospital can receive depending on how many things on the checklist they can complete. The silver standard is for practices that meet the essential standard criteria for a CFP[2]. Gold standard is for practices that have incorporated the optimum level of the CFP criteria[2].

After reviewing the check list, the manager or owner should determine which level they are able to qualify for. Once they have made the decision, they need to review the checklist and start working on it. The process can take weeks or months depending on the time that the hospital is able to devote to completing the checklist. Sometimes hospitals have already completed things on the checklist without even realizing so it might not take as long as you think. The website will automatically save your progress while you are going through the CFP process so you can easily pick up where you left off.

The 10 Topic Areas in the CFP checklist:

- Staff training & continuing education
- Veterinary Practice Premises| Waiting Area
- Feline Handling & Interactions with Clients
- Examination rooms|Clinical records

- Hospitalization & Boarding of Cats
- Pain Management|Operating room & anesthesia
- Surgical Equipment|Dentistry
- Diagnostic Imaging|Laboratory Facilities
- Treatment|Health & Safety
- Feline Preventive Healthcare Individualized by Life Stages

There are several things on the check list that might be overwhelming to the managers and other leaders in the hospital. The manager will need to select a cat advocate to help complete the things on the checklist and assist with the training. The cat advocate will need to be someone who can get things done and truly believes in the CFP process. When reviewing the check list, they will need to determine any obstacle that the hospital might face and see if there is a way to work around it.

There are a few challenges that hospitals have with becoming a CFP. One of them is creating a more cat friendly lobby. AAFP does not require that you have a separate lobby for your cat patients, other options include creating a partition between the dogs & cats, taking the cats straight into exam rooms, or having your cat patient come on different days[2], The AAFP website has some good examples of alternative options for your lobby.

Another challenge is staff training. AAFP requires the staff to be trained on the feline friendly guidelines and for some staff members this could be a new concept. The key to making it easier for cats, is to minimize the amount of stress they are exposed to. For some hospitals this requires a completely new approach by all team members. From the receptionists taking the phone calls, to the technician working with the cat everyone needs to be thoroughly trained on the best way to handle cats and their visits.

What are the benefits to becoming cat friendly?
As discussed previously creating a calmer environment for cats is the goal of becoming a CFP but how does that affect the hospitals bottom line?

A CFP practice is more appealing to cat owners and over 80% of hospitals said they gained new feline patients because of becoming cat friendly[2]. AAFP provides a large amount of marketing material to show your clients and potential clients that you are cat friendly. CFP practices all get certificates showing they are cat friendly they can place in their lobby or visible area to show clients. There are other types of signage clients can have in their hospital that are available from AAFP or they can make themselves. They can put the cat friendly notices on their window as well as promote on their social media. By becoming known as a cat friendly hospital more cat clients will be encouraged to visit.

In addition to the appeal to clients, the knowledge and abilities of the team members can increase significantly. 93% of CFP said that they saw improved knowledge in feline care among practice staff[2].
By training the team on cat behavior it became easier for them to not only recognize the cat's triggers but in many cases prevent them. Training the team more is also beneficial to help decrease staff injuries. In the 2018 survey results 61% of hospitals said that they saw a decrease in injuries[2].

There are also a lot of opportunity to increase feline visits by becoming CFP.

There are a few different ways to do this:
1. Focus on the hidden feline patient. A large percentage of clients bring in their dogs for regular veterinary care but not their cats! It is important to identify which clients have both cats and dogs in your software. On your new client form have clients list all their pets so they can be entered into your database. When a client comes in with their dog have the staff or doctor review the record and see if there is a hidden feline patient that you have never seen or rarely see. This allows you to have a discussion with the client about their cats' veterinary needs. Over 60% of your clients know their cats get stressed out by coming to the vet and 39% of them will not bring their cat in unless they are really sick[1] It is important to have a conversation with them about why their cat needs veterinary care and how you can help make the visit less stressful.
2. By following the CFP guidelines for senior care, you recommend that the come in twice a year, instead of just once. This will increase their visits and potentially catch diseases early.

One of most important results of becoming a CFP hospital is an increase in revenue. In the 2018 survey 79% of hospitals reported an increase in revenue[2] by becoming a CFP.

Conclusion

Over the past few years the majority of hospitals who have become CFP have seen positive results. Based on the 2018 CFP survey 98% of CFP practices would recommend it to other veterinary professionals.

References

1. K Felstad, Bayer Veterinary Usage Study, 2011
2. American Association of Feline Practitioners, Cat Friendly Practice®, https://catvets.com/. 2019

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Team Building: Create Stronger Practice Teams

Melissa Tompkins, BS, CVPM

Introduction
In this interactive presentation attendees will learn how to use team meetings to help build a stronger team as well introduce/maintain the hospitals' core values. We will discuss why it is important to have core values that your team members believe in. We will also discuss not only the important of having regularly team meetings but how to make effective

Why should you have core values? There are a lot of reasons to have core values, but the most important one is so that all your team member can understand and communicate the hospital's message.

How do you create core values? The practice owner and manager should sit down and focus on what their vision is for the hospital. What type of hospital do you want to be? What values do you want your employees to have? What values do you want your clients to see? Once the leadership has discussed the vision, they should sit down with the team and talk about how to reach that vision.

When you sit down to talk about your vision with the team you should start by asking them write down what the vision means to them. When you have the team help create the vision and core values, they are more likely to believe in them. You could have them write little messages on post-it notes and put them on a poster board. Quail Animal Hospital in Irvine, CA put the poster board in their breakroom as a reminder of all the good things the team felt about the hospital. Foothill Animal Hospital in Lake Forest, CA has their vision statement on their website "where your pets are treated like our own." Orange County Emergency Pet Clinic in Garden Grove, CA took their core values and put them on the wall of their breakroom as well. They wanted the employees to be reminded of "why they do what they do" on a regular basis.

Team meetings
Why have team meetings? Communication, communication, communication!

Team meetings are an essential part of a hospital success. Most well-managed practices have meetings at least monthly. The purpose of the meeting should not only be to convey important messages to the team but to continue the feeling of community within the team.

Planning the meeting
When planning the meeting always start with an agenda. Collect information from the all the leaders in the hospital and ask the team to contribute ideas well. If you make it easy for the team to submit ideas for the meeting, they are more likely to do so. I can't tell you the amount of times I learned something was broken because someone wrote it down to be discussed in the meeting.

After you have your agenda, make sure that you have selected the best time and location to have the meeting. This is going to be different for every hospital.

In addition to all the individual topics & training, think about what core values will be discussed in the meeting. The hospitals core values and the vision of the hospital should be discussed in almost every meeting. This doesn't mean that you need to read them out loud every time, but they should be part of the conversation. A good way of doing this is to bring up positive things that have happened and talk about how that relates back to the core values. You can also bring up negative things that have happened as well and discuss if the core values were followed or not.

By discussing the core values regularly, it becomes part of the culture for the employees to make decisions based on the core values. A lot of times we forget why "we do what we do" and this is a great way of reminding them.

A fun way to remember the core values & make the meetings enjoyable is to use team building games in the meetings. There are a lot of different games that can be used for team building activities.

Why use games?
- Icebreakers, especially when you have new people or department changes within the hospital
- To create the team identity
- To demonstrate the value of teamwork

- To stimulate the appreciation of diversity
- To build mutual support & trust
- To improve team functioning
- To stimulate the team members recognition for change
- To surface hidden problems
- To interject great energy into team meetings

A general rule for team building to select the specific game carefully. Make sure the game fits your team's general nature and character, the objectives for the team's meeting and the participants themselves. Make sure you have an objective and that you clearly communicate that objective to the team. Have a back-up plan. In case the game has problems, or the team is unresponsive to it. Pretest the game. Make sure that it won't be a waste of time and that it makes sense.

Tips for using team building games:

- Choose low-risk activities
- Be brief & selective
- Be prepared
- Anticipate some resistance and prepare for it
- Once game is completed remind them of the message of the game
    - This should always go back to your core values

Be cautious of games that requires the use of a lot of props. Be aware of your time requirements too so that you don't run out of time to complete the game, or that it is too short for the allotted meeting time. Also, make sure that it is not overly complicated or difficult to follow.

Ideas for team building games that relate to core values

The Big Book of Team Building Games[1] a good resource to find unique and fun games for your team. This book includes trust-building activities, team spirit exercises, and other fun things to do.

"Getting to know you"[1] is a great game to play with a new team or when trying to build community within an existing team. Have each team member share something fun about themselves that most of the team doesn't know. I have done this several times and learned amazing things about my team members.

"So much in common."[1] The objective is to demonstrate just how much everyone can have in common. In this game you pair people up into groups of two. Instruct them to find out as many things as they can, that the two of them have in common. Give them 2-3 minutes to do this. At the end of the 3 minutes ask who found the most things in common and you could even give a prize for that (don't tell them a head of time if you are going to give a prize). Talk about what types of things they have in common and how that can relate to them working together in the future.

"The I's Have it."[1] The objective is to show that team members tend to be more self-centered than they might realize and demonstrate the importance of focusing on other people. At the beginning of the meeting have a discussion on inter-personal skills or communication. In this discussion mention that many of us forget about focusing on others when we are having conversations. Then tell the team to find a partner and for the next two minutes talk about anything in the world they want to discuss, but that they cannot use the word "I". After the two minutes is up have them share if anyone was able to talk for two minutes without using the word "I". Discuss how we can phrase communications to better focus on the other person.

Conclusion

Creating core values and training the team on them goes a long way to cultivating a dynamic culture within the hospital. This culture can many times lead to the success or failure of a hospital and should be focused on.

References

1. J. Newstrom & E. Scannell, The Big Book of Team Building Games, McGraw Hill, 1998

NOTES:

American Association of Feline Practitioners
2019 Conference ● October 31 – November 3, 2019 ● San Francisco, CA

Feline Infectious Upper Respiratory Disease: What Every Veterinarian Should Know

Annette Litster, BVSc, PhD, FANZCVS (Feline Medicine), MMedSci (Clinical Epidemiology)

Background and Etiological Agents

Upper respiratory tract disease (URTD) and it is the most common disease reported among the approximately 2 million to 6 million cats housed in US shelters annually and is often a cause of euthanasia because of the risks of transmission of infection throughout the shelter population and the negative effects on adoptability of infected cats. The combination of stress associated with relocation to a shelter, the presence of large numbers of cats in potentially crowded conditions, and variability in immune status increases morbidity and mortality rates attributed to URTD in shelter cats. Managing and treating feline URTD is challenging in a multi-cat environment because it is highly infectious and readily spread by direct cat-to-cat contact or indirectly by fomites. The most common pathogens are feline herpesvirus type 1 (FHV-1), feline calicivirus (FCV), *Mycoplasma felis*, *Bordetella bronchiseptica*, and *Chlamydia felis*. The isolation of FCV, *Mycoplasma* spp., and *C. felis* are significantly associated with clinical signs of URTD, including conjunctivitis, ocular or nasal discharge, gingivitis, and oral vesicles. Four studies have yielded statistical evidence of an association between clinical signs of URTD and the presence of FHV, FCV, *Mycoplasma* spp., *C. felis*, and *B bronchiseptica*, and investigators of one study reported more severe clinical signs in cats infected with multiple pathogens. Cats that appear to be clinically recovered from URTD may remain persistently infected and serve as sources of infectious agents in the shelter. Whereas primary viral infections with FHV and FCV are prevalent in cats with URTD, secondary bacterial invasion by *Pasteurella* spp.*, Escherichia coli*, *Staphylococcus* spp., *Streptococcus* spp., or *Micrococcus* spp. regularly develops (Litster et al., 2012).

Antimicrobial Treatment Options for Bacterial URTD

To prevent the development of resistance to antimicrobials by infectious agents, drug selection should be specific to the individual cat and infectious agent being treated and informed by appropriate diagnostic testing whenever possible. Additionally, cats should be carefully monitored for response to treatment; lack of response within 7-10 days could indicate additional medical or drug-related problems that require further diagnostic workup for specific identification (Lappin et al. 2017). Doxycycline (5mg/kg q12h or 10mg/kg q24h) is a good first choice for acute bacterial URTD in cats because it is well tolerated by most cats and has activity against *Mycoplasma felis*, *B. bronchiseptica* and *Chlamydia felis* (Lappin et al. 2017). Doxycycline formulations approved for use in cats are preferred if available and can be used without tooth enamel discoloration in kittens over 4 weeks of age. Compounded doxycycline suspensions can violate prescription regulations in some countries, including the USA (Lappin et al. 2017), and variable loss of drug activity has been reported after 7 days with aqueous formulations (Papich et al. 2013). If *Mycoplasma felis* and/or *Chlamydia felis* infections are not suspected, amoxicillin (22mg/kg q12h or amoxicillin–clavulanate 12.5mg/kg q12h) is an acceptable fist-line option for the treatment of acute bacterial URTD (Lappin et al. 2017).

Fluoroquinolones, β-Lactams, tetracyclines, and broad-spectrum macrolide antimicrobials (e.g., azithromycin) have therefore been used as part of the treatment of cats with suspected bacterial URTD. Amoxicillin-clavulanic acid is effective *in vitro* against *C. felis, B. bronchiseptica*, *Staphylococcus* spp., and *Streptococcus* spp., but is less effective *in vitro* against most Gram-negative isolates. Doxycycline is reported to be effective in vitro against *Mycoplasma* spp., *C. felis,* and *B. bronchiseptica* and is efficacious for the treatment of *Pasteurella* spp. infections. However, the results of a study of *in vitro* antimicrobial susceptibility of bacterial isolates cultured from respiratory samples from cats with respiratory tract disease indicated that the overall efficacy of doxycycline was relatively poor.

Cefovecin is a semisynthetic third-generation cephalosporin with bactericidal activity against both gram-positive and gram-negative pathogens. It is formulated as an aqueous solution and is rapidly absorbed in cats after SC injection. After absorption, cefovecin is slowly eliminated and produces long-lasting circulating concentrations of unbound drug in extracellular fluid that permits a 14-day dosing interval. Cefovecin's prolonged effective plasma concentrations and SC route of administration facilitate compliance and could avoid potential stress associated with repeated oral antimicrobial administration in cats. However, in a large study of feline bacterial respiratory infections, cephalexin (a second-generation cephalosporin) was ranked second only to enrofloxacin for *in vitro* efficacy against the most frequently isolated bacterial species. *Bordetella*, *Mycoplasma*, and *Chlamydia* spp. were not among the most frequently isolated bacterial species in the population examined in that study, thus explaining this unexpected finding because cephalexin is not expected to be an effective treatment for these infections (Litster et al., 2012).

Pradofloxacin, a novel third-generation fluoroquinolone, has been used to treat feline URTD in several published studies. In one study of cats with bacterial rhinitis, treatment with either oral pradofloxacin or amoxicillin produced similar results, while another study of cats with URTD treated with either pradofloxacin or doxycycline reported both

clinical resolution and clearance of *Mycoplasma* infection in both groups, but doxycycline had superior efficacy for the clearance of *Chlamydia felis* infections (Sykes and Blondeau, 2014).

Table 1. Commonly used antimicrobial treatment options for feline bacterial upper respiratory tract disease (Lappin et al. 2017).

Isolate	**Amoxicillin/ clavulanic acid (12.5mg/kg q12h PO)**	**Cefovecin (8mg/kg SC; 14 day duration of action)**	**Doxycycline (5mg/kg q12h PO) Minocycline (8.8 mg/kg q24h PO)**	**Azithromycin (5-10mg/kg q12h on Day 1, then q72h PO)**	**Fluoroquinolones - Marbofloxacin (2.7-5.5mg/kg q24h PO) Pradofloxacin (5mg/kg q24h PO for tablets; 7.5mg/kg q24h PO for oral suspension) Enrofloxacin[a] (5mg/kg q24h PO)**
Bordetella bronchiseptica	First-line option	Ineffective	Likely to be effective	Refer to specific infection susceptibility profiles	Likely to be effective
Chlamydia felis	Inferior to other drugs	Ineffective	Likely to be effective	Unlikely to be effective	Likely to be effective
Mycoplasma spp.	Ineffective	Ineffective	Likely to be effective	Refer to specific infection susceptibility profiles	Likely to be effective
Staphylococcus spp. *Streptococcus* spp.	First-line option	Likely to be effective	Refer to specific infection susceptibility profiles	Refer to specific infection susceptibility profiles	Likely to be effective

PO, Per os; SC, Subcutaneous

[a] Has been associated with retinal degeneration in cats (Gelatt et al. 2001)

***Mycoplasma* URTD**

A study of URTD in shelter cats reported that *Mycoplasma* spp. was the most common bacterial isolate recovered from conjunctival and nasal swabs (22/48 cats, 46%; Kompare et al., 2013), echoing the findings of an earlier study that recorded *Mycoplasma* spp. in 60.7% of shelter cats with respiratory signs. *Mycoplasma* spp. are degenerate, obligatory parasitic bacteria, bound by a single limiting cell membrane. *Mycoplasma* spp. have been recovered from both the normal flora of the upper respiratory tract, conjunctiva, and genital tract of cats. In addition, *Mycoplasma felis* has also been implicated as the cause of URTD, conjunctivitis, and polyarthritis. In one study, the isolation of *Mycoplasma* spp. from oropharyngeal swabs in cats was significantly associated with URTD. *Mycoplasma felis, Mycoplasma gateae, Mycoplasma feliminutum* and *Mycoplasma arginini* have also been isolated from the upper respiratory tracts of healthy cats; therefore as long as diagnostic methods specifically target *Mycoplasma felis* are used, the presence of other *Mycoplasma* species should not produce false positive results. Whether acting as a primary pathogen or secondary opportunistic invader, *Mycoplasma* spp. is an important infectious agent in feline URTD.

Mycoplasmas are susceptible to fluoroquinolones and tetracyclines *in vitro* and *in vivo*. The tetracyclines (tetracycline, oxytetracycline, minocycline, and doxycycline) are bacteriostatic antibiotics that interfere with bacterial protein synthesis. Doxycycline is known for its broad-spectrum efficacy and higher intracellular concentrations than other tetracyclines. In cats, doxycycline is indicated for the treatment of *Mycoplasma* spp. infections as well as *Bordetella bronchiseptica* and *Chlamydia felis* URT infections. However, the tablet form of the drug has marked ulcerogenic properties in cats and needs to be used with caution, preferably followed by water or a food swallow immediately after administration.

A study examining the efficacy of doxycycline for the treatment of feline URTD suggested that a 42-day course length was necessary for effective treatment of *Mycoplasma* spp. because of prolonged positive PCR results from conjunctival swabs in a small number of cats (positive PCR detection after 28 days in 3/20 cats). However, since *Mycoplasma* infections of animal and humans persist in their host for extended periods after infection, resisting clearance using intracellular localization, immunomodulatory effects, and surface antigen variations, resolution of clinical signs might be a more important and practical determinant of treatment efficacy than negative PCR results.

Also, given the inherent challenges for owner compliance with long courses of oral medication and the stress of medication administration for cats, reducing treatment length below the currently recommended 42 days could have practical and economic benefits (Kompare et al., 2013).

Antiviral Agents

Antiviral drugs for feline URTD are directed against FHV-1, but since antiviral agents have not been specifically developed for cats or for the treatment of FHV-1, drugs with activity against closely related human herpesviruses and tested for safety in cats, such as oral famciclovir, topical ophthalmic idoxuridine and cidofovir, are sometimes used. Importantly, it should not be assumed that antiviral drugs that are safe and efficacious for human herpesvirus infections are safe for cats or effective against FHV-1. Available drugs cannot clear infection; they merely aim to reduce viral replication, thereby reducing the severity and/or duration of clinical signs. Because of this, if the decision is made to use antiviral drugs because infection is severe, persistent or recurrent, correct dose rate and frequency are critical to successful therapy. Clear guidelines for course length have not been developed, but therapy should ideally be continued for a period after the resolution of clinical signs. Since the clinical signs of FHV-1 infection are often self-limiting, clinical trials of antiviral therapies should be placebo-controlled if they are to provide reliable information (Thomasy and Maggs, 2016).

Famciclovir for the Treatment of Feline Herpesvirus

Compared to humans, famciclovir has poor bioavailability in the cat that can vary significantly between individual cats. Famciclovir undergoes di-acetylation in the blood, and then is oxidized to penciclovir in the liver, but feline hepatic aldehyde oxidase has negligible activity. At a dosage of 15mg/kg, peak plasma levels of 350+/-180 ng/mL penciclovir were detected at 4.6 +/- 1.8 hours, and the elimination half-life was 3.1 +/- 0.9 hours. Cats given 40 mg/kg, a 2.7 fold increase, displayed a 4-fold increase in penciclovir Cmax. Increasing the dosage from 40mg/kg to 90mg/kg gave no corresponding increase in peak penciclovir plasma concentration. In prior studies, famciclovir was found to reduce clinical signs caused by FHV-1 as well as decrease viral shedding. While tear concentrations of famciclovir in cats treated with 40 mg/kg are likely to be effective in treating ocular clinical signs associated with FHV-1, antibiotics and or tear replacement products might be necessary due to alterations of the quality of tear film produced by reduced goblet cell density. As in humans, the principle route of elimination is via the kidneys (Thomasy and Maggs, 2016).

A retrospective case series (uncontrolled) studied 59 client-owned cats and kittens with chronic (at least 180 days' duration) clinical signs of URTD prior to oral famciclovir treatment, and treated with low- (approximately 40 mg/kg q8h) or high-dose oral famciclovir (approximately 90 mg/kg q8h), was more promising. Most cat owners and attending veterinarians observed clinical improvement, especially in the high-dose group, which had higher clinical improvement rates, lower response times and shorter treatment durations than the low-dose group. Cat owners reported temporary (n=8/32, 25%) or permanent (n=17/32, 53%) improvement of clinical signs. Famciclovir course length was at the discretion of the attending veterinarian; one course was administered in 44/59 (75%) cats and two or three courses in 15/59 (25%) cats. Adverse effects, including diarrhea, vomiting, anorexia and polydipsia were reported in 10 adult cats at 3-36 days after the initiation of treatment (Thomasy et al. 2016).

In a published two part, randomized, masked, placebo controlled study, cats received a single dose of 125 mg famciclovir (*n* = 43) or placebo (*n* = 43; pilot study), or 500 mg famciclovir (*n* = 41) or placebo (*n* = 40; clinical trial) on entering a shelter (Litster et al., 2015). The abstract reports the results as follows –

FHV-1 PCR testing was performed, bodyweight and food intake were recorded, and signs of respiratory disease were scored prior to and 7 days following treatment. FHV-1 DNA was detected in 40% of cats in both parts at study entry. In the pilot study, ocular and nasal discharge scores increased from days 1 to 7 in famciclovir and placebo treated cats. Sneezing scores increased and bodyweight decreased in famciclovir-treated cats. The proportion of cats in which FHV-1 DNA was detected increased over time in all cats in the pilot study. In the clinical trial, food intake and median clinical disease scores for nasal discharge and sneezing increased from days 1 to 7 in both groups and demeanor scores worsened in famciclovir-treated cats. The proportion of cats shedding FHV-1 DNA was greater on day 7 than on day 1 in cats receiving 500 mg famciclovir. A single dose of famciclovir (125 or 500 mg) administered at shelter intake was not efficacious in a feline population in which 40% were already shedding FHV-1.

L-lysine

Dietary L-lysine supplements have been used extensively for the prevention and treatment of FHV-1 infection in the belief that it lowers plasma and tissue arginine concentrations by one or more unconfirmed cellular mechanisms, thereby limiting viral replication, since FHV-1 requires arginine for protein synthesis. Clinical trials of L-lysine supplementation in cats with FHV-1 have produced conflicting results, but a recent systematic review of the evidence for L-lysine supplementation concluded that clinical trials with cats had failed to show efficacy and that in vitro experiments did not demonstrate that excess L-lysine inhibited viral replication (Bol and Bunnick, 2015). Another recent review concluded that there was some evidence that bolus oral administration of L-lysine might decrease

FHV-1 shedding in latently infected cats and reduce clinical signs in cats on their first exposure to the virus. However, the point was also made that the stress of oral bolus administration might negate any beneficial effects of supplementation in shelter cats (Thomasy and Maggs, 2016).

The published evidence for the efficacy of oral L-lysine supplementation in cats at risk of FHV-1 exposure or reactivation is conflicting at best (Bol and Bunnick, 2015). Since it diverts shelter resources (both funds and labor) from other measures more likely to reduce URTD rates, and its administration is likely to be stressful for cats, it is not a recommended shelter protocol.

Topical Ophthalmic Antiviral Drugs

Topical ophthalmic preparations for herpetic keratitis include idoxuridine (0.1% ophthalmic solution or 0.5% ointment, q4-6h; available only from compounding pharmacies in the USA) and cidofovir (0.1% ophthalmic solution q12h; commercially available in injectable rather than topical ophthalmic form in the USA; Thomasy and Maggs, 2016). Idoxuridine is relatively cheap and well tolerated by most cats. A case series study reported improvement or resolution of clinical signs in three cats and no improvement or worsening in four cats treated with topical ophthalmic idoxuridine (Stiles 1995). A randomized, placebo controlled study of 0.5% ophthalmic solution of cidofovir compounded in methylcellulose and applied twice daily to cats experimentally infected with FHV-1 reported reduced viral shedding and clinical improvement, but since nasolacrimal stenosis has been reported in humans receiving topical cidofovir, treated cats should be monitored closely for signs of problems with tear drainage (Stiles 1995).

Table 2: Feline Viral URTD therapeutics (Table modified by courtesy Dr. Martin Coster, Purdue University)

Drug	Pathogen	Advantages	Disadvantages
Trifluridine Viroptic topical ophthalmic drops	FHV-1	Highest in-vitro efficacy	Local irritation, q4-6h, $
Idoxuridine Compounded topical ophthalmic drops/ointment (0.5%)	FHV-1	Effective	q4-6h
Cidofovir Compounded topical ophthalmic drops (0.5%)	FHV-1	q12h Alternative	Less effective?
Acyclovir Zovirax; Oral/injectable/topical	FHV-1	Available	Ineffective Systemic side effects – monitor CBC weekly
Famciclovir Oral; metabolized to penciclovir	FHV-1	Safe; efficacy?	$$$, efficacy/optimal dose rate unproven in RCT 90mg/kg PO q12h? 40 mg/kg q8h?
Feline Recombinant Interferon Injectable	FHV-1, FCV	Synergy with other drugs?	FDA permit required

Symptomatic Therapy

While therapy directed at specific FURD pathogens, such as anti-viral or antimicrobial drugs, is sometimes warranted, supportive care to address the clinical signs of disease should be provided whenever possible. Fluid therapy with a balanced electrolyte solution such as lactated Ringer's solution can be administered either subcutaneously or intravenously, and is important to correct dehydration resulting from fluid losses in ocular, nasal and oral discharges and lack of fluid intake in anorexic or inappetent cats. Intravenous fluids should always be administered under the supervision of a veterinarian to reduce the risk of catheter infections, fluid overload or electrolyte disturbances.

Pain relief should be considered on an individual cat basis, especially if there is evidence of oral or corneal ulceration. Appropriate analgesic protocols should be initiated promptly by a veterinarian and cats should be monitored often to ensure that therapeutic efficacy is achieved. Non-steroidal anti-inflammatory drugs can also be used to treat fever and oral or ocular pain (Radford et al., 2009), but caution should be exercised in cats with evidence of clinical or subclinical dehydration, renal, hepatic or gastrointestinal disease or clotting abnormalities Griffin et al., 2016). Additionally, cat comfort should be prioritized by gentle cleaning of crusted ocular and nasal discharges using warm saline and a soft disposable cloth. Ideally, isolation ward housing should be warm and cozy, with soft bedding and toys and a hiding place in each cage that also allows the cat to be seen, so behavioral and clinical status can be monitored. Bedding and toys can be disposable, or washed in hot water and soaked in appropriate disinfectant, such as 1:32 solution of 5.25% household bleach, potassium peroxymonosulfate or

accelerated hydrogen peroxide, so that non-enveloped viruses such as FCV are destroyed (ASPCA, 2017). Some cats also benefit from periods of nebulization using 0.9% saline (e.g. 15-20 minutes 3-4 times a day with the cage door covered in a towel to keep the steam in) to rehydrate upper respiratory tract mucous membranes (Thiry et al., 2009).

Many cats with URTD are inappetent or anorexic because they have lost their sense of smell or because of painful oral ulceration, but the immune system needs to be supported with protein and calories if it is to effectively fight infection. If a cat has not eaten for 3 days, a feeding tube should be placed by a veterinarian and enteral nutrition commenced (Thiry et al., 2009). Return to normal eating is an important milestone and some cats benefit from appetite stimulants such as mirtazapine (3–4 mg per cat PO q72h) or cyproheptadine (2–4 mg/cat q12–24h; Plumb, 2015 to help them commence eating voluntarily once recovery is underway (Radford et al., 2009).

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NOTES:

It's a New World: Update on Feline Retrovirus Testing

Susan Little, DVM, DABVP (Feline)

Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are retroviruses that represent two of the most important infectious diseases of cats worldwide. The most important measure for the control of FeLV and FIV is the identification and segregation of infected cats. Thus, the American Association of Feline Practitioners recommends screening all cats for infection at the time they are first acquired, prior to initial vaccination against FeLV (or FIV in countries where a vaccine is available), following potential exposure to infected cats, or in cats with clinical signs. The seroprevalence of FIV is highly variable among geographic regions. Estimates in cats without clinical signs range from 1-14% and estimates in sick cats may be as high as 44%. The seroprevalence of FeLV also varies widely, from less than 1% to over 20%. A comprehensive review of clinical aspects of retrovirus infection has been published.[1]

Point-of-care (POC) tests based on enzyme-linked immunosorbent assay (ELISA) or immunochromatographic (IC) methods are routinely used for serologic detection of FeLV antigen (p27) and FIV antibodies (p15, p24, gp 40; varies by assay) in whole blood, serum, or plasma. Referral laboratories also offer screening tests for FeLV and FIV. FeLV p27 antigen appears early in the viremic phase of infection, typically within 30 days of exposure. FIV antibodies may not appear for 60 days or longer after exposure.

Studies evaluating the performance of currently available POC test kits are available.[2-4] Referral laboratories offer follow up or second tier tests: polymerase chain reaction (PCR), immunofluorescent antibody (IFA), and Western blot (WB).

A positive result on a screening test has clinically important consequences; therefore, follow up testing is recommended especially in low-risk cats (e.g., apparently healthy cats, indoor-only cats) where the likelihood of a false positive result is greater than in a higher risk cat (e.g., sick, outdoor access). Negative test results are generally highly reliable (especially in clinically well, low risk lifestyle cats) as highly sensitive POC tests are available.

Cats destined to be blood donors represent a special case where the utmost precautions must be taken to ensure they do not have retrovirus infection. In one study, 10 of 15 cats receiving blood transfusions from donor cats negative for FeLV p27 antigen but FeLV provirus-positive by PCR developed active FeLV infections.[5] A sensitive PCR test for FeLV should be performed on any cat serving as a blood donor (even if the donor is vaccinated against FeLV) to prevent inadvertent transmission to recipients.

It may not be possible to determine FeLV or FIV infection status based on the results of a single test performed at a single time point.

What To Do When A Cat Tests Positive For Fiv Antibody

Positive screening test results must be interpreted carefully in kittens as they may have acquired antibodies from an infected (or FIV-vaccinated) queen via colostrum. In a study of 55 kittens born to FIV-vaccinated queens, all kittens tested positive for FIV antibodies shortly after birth and for the first few weeks of life.[6] By 12 weeks of age, all kittens tested FIV antibody-negative. Therefore, FIV antibody-positive kittens should be re-tested in one month with a POC test to determine their status. Repeat testing may be required over time to clarify status. Kittens that are negative on a follow up test are likely not infected. Kittens persistently testing FIV antibody-positive by 5-6 months of age are likely truly infected.

Adult cats (>6 months of age) are more likely to be infected with FIV than kittens. A positive antibody test result (using a reliable test) in a cat with compatible clinical signs is likely to be correct, provided the cat has no history of FIV vaccination. Test interference from FIV vaccination has been of importance over the last 15 years as vaccination produces antibodies detected by some POC tests and by WB. Antibodies due to vaccination may persist for years after the last vaccine is administered and are also acquired by kittens nursing on vaccinated queens. Certain POC kits (Witness FeLV-FIV, Anigen Rapid FeLV/FIV) seem to be able to identify natural FIV infection regardless of vaccination history, likely because they target gp40 antibodies.[2] Therefore, re-testing with a different POC test or a validated PCR test may be necessary in FIV antibody-positive cats with a history of FIV vaccination.

In the past, WB was considered the best follow up test for FIV, but research suggests it does not perform as well as some POC tests.[7] PCR tests for FIV should not be influenced by maternally acquired antibodies in kittens or by FIV vaccination. The published studies have all evaluated the same quantitative real-time PCR that detects both proviral

DNA and viral RNA in peripheral blood leukocytes (IDEXX FIV RealPCR).[8] Therefore, a validated PCR test is another option for follow up testing of kittens and adult cats and can be performed immediately. If the PCR test is positive, the cat is likely truly infected with FIV. If the PCR test is negative (discordant test results), further testing with both an ELISA or IC test and PCR may be required to clarify status. PCR tests may be falsely negative for FIV if the level of viral nucleic acid in the sample is below the limit of detection, or if the sample contains a strain of virus that is not detected by the primers used.

What To Do When A Cat Tests Positive For Felv Antigen

Screening test results for FeLV antigen are not affected by maternally acquired immunity in kittens. Adult cats and kittens with a positive screening test that are clinically well or at low risk of infection should have follow up testing performed to clarify infection status. In some cases, multiple tests must be performed over time. If the cat was tested with a POC test, a sample should be sent to a referral lab for a plate assay for FeLV antigen or for PCR testing. Repeat testing may clarify the cat's status.

Regressively infected cats can be identified using a combination of p27 antigen and provirus PCR tests. The pattern of test results is influenced by the sensitivity of available tests which varies regionally and among laboratories. Due to differences in tests, regressive infection in Europe is typically characterized by a negative or transiently positive antigen test and positive proviral PCR while in North America, regressive infection is more likely to be an antigen positive, PCR negative pattern. Cats that initially test positive by both p27 antigen and PCR can transition to a regressive infection pattern usually within 16 weeks post-infection.

What To Do When A Cat Tests Negative For Fiv Antibody Or Felv Antigen

A negative test result is highly reliable (especially in apparently healthy cats and kittens) and does not typically require follow up testing. Follow up testing may be considered in certain circumstances, such as cats with suggestive clinical signs or cats destined for a breeding program or blood donor program.

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NOTES:

Maintain Muscle Mass While Feeding Feline Renal Therapeutic Diets

Amy Farcas, DVM, MS, DACVN

Introduction

There appears to be two camps of veterinarians with strong opinions recommending nutritional management of chronic kidney disease (CKD) in cats, particularly with respect to the issue of protein intake. One has a primary consideration of dietary protein contributing to uremia, and the other has maintenance of lean body mass (LBM) as its focus. These two philosophies are frequently discussed as if they are completely at odds with each other. The reality is that with some careful consideration, concerns for uremia can be managed without sacrificing LBM. It starts with a detailed nutritional assessment[1].

Clarifying terminology

For the purpose of this discussion, the term restriction is used to refer to reduction of nutrient intake below a patient's minimal requirement. Phosphorus restriction is generally indicated in most patients with CKD due to their abnormal phosphorus retention. Moderation is the term that will be used to refer to reduction of a patient's intake of a nutrient to that which meets, but does not significantly exceed, their requirement for that nutrient. The author is not aware that these terms are formalized with these definitions elsewhere, though it may reduce the disagreement on the topic of protein intake of cats with CKD if it were. Within this discussion, requirements refer to National Research Council (NRC) minimal requirement[2] (MR). It is worth note that IRIS treatment guidelines do not reference "protein restriction" "protein reduction", or "protein moderation" in any way; recommendations refer to feeding "renal therapeutic diets," but do not discuss protein content of these diets.

Nutritional assessment

Weight, body condition score, and muscle condition score

Nutritional assessment includes obtaining body condition score (BCS)[3], and muscle condition score (MCS)[4] for each patient, in addition to body weight (BW) and complete physical examination. This allows for the patient's minimal protein requirement to be determined based on NRC MR for protein (~4 g protein/BW (kg)^(2/3)). Even when aiming for as little protein excess as possible, most nutritionists provide some "buffer" to allow for inaccuracies in diet reporting, variation in digestibility, potential for increased requirements, individual variation, and other possible sources of inaccuracy, as providing slightly more protein than intended is likely not worth the risk of the detrimental opposite outcome of protein malnutrition. This highlights the need for accurate data collection with respect to current diet amount and type so that current caloric (and protein) intakes can be determined. While the patient's maintenance energy requirement (MER) can be calculated from their current weight and BCS, the result of this calculation yields the center of a bell curve, with any individual cat having an actual MER that is 50% above or below this calculated value. For this reason, diet history may be more useful.

Diet history

Collecting detailed information on the patient's current diet (including main meals, treats, pill-administration aids, training treats, edible chews, scavenged food, hunted food, etc.) is especially useful in a patient where dietary protein intake adjustment is being considered. Having that patient's current caloric intake in hand, in addition to knowledge of whether they are gaining, losing, or maintaining BW on that energy intake are key to making a diet change recommendation. The patient must consume both an appropriate amount of energy (calories) and protein in order to maintain BW and LBM (and to generally do well clinically). In patients where current diet information isn't available, the calculated MER can be used for decision-making, but the clinician should keep in mind that the plan may require additional adjustments. More information is always better.

Feeding recommendations based on International Renal Interest Society (IRIS) guidelines (in brief)[5]

IRIS stage 1 CKD: introduction of long-chain omega- polyunsaturated fatty acids (EPA+DHA)

IRIS stage 2 CKD: above, plus phosphate binders or phosphorus-restricted diet as appropriate to achieve target serum phosphorus concentrations. Protein moderation is not necessarily indicated, though introduction of protein moderation at this stage may have better acceptance than when patient is having uremic signs at stage 3, when protein moderation actually is indicated.

IRIS stage 3 and 4 CKD: above, plus protein moderation.

All stages: adjustment of electrolyte intake/supplementation as appropriate.

Using nutritional assessment data and IRIS recommendations to direct diet recommendation

According to the above, the clinician has now determined the patient's caloric and protein requirement, and the relevant nutritional parameters; particularly whether protein moderation, phosphorus restriction and/or binders,

EPA+DHA supplementation, and other electrolyte adjustments are indicated. With the assessment completed, a plan can be formed.

Selecting a diet

Commercial renal therapeutic diets

These diets generally provide 23-28% of calories from protein and provide 0.5-1 g phosphorus per 1000 kcal. Presently, there are many options available in the marketplace as development of food aversion is somewhat common in this patient population. While this nutritional profile generally suits most cats through most stages of CKD, this ratio of protein to calories will not necessarily be the best fit for every patient. Particularly housecats with very low energy requirements (actual MER <~75% of calculated MER), when the patient eats an amount of food that meets their energy requirement, they do not consume enough protein. In these cats, a higher-(than this)-protein diet is needed to avoid protein malnutrition and loss of LBM. Some therapeutic diet manufacturers now make "early renal" diets that are not as low in protein as the rest of the group of renal therapeutic diets. Achieving sufficient phosphorus restriction outside of the category of "therapeutic renal diets" may be challenging, and a customized home-prepared diet may be a better option if the cat (and owner) will transition to this.

Home-prepared renal therapeutic diets

Many pet owners have selected specific commercial maintenance diets for their cats based on philosophical considerations, many, but not all of which, may be driven by misunderstanding of pet food marketing claims and phrases. A gentle and supportive "myth-busting" session may be in order. Many of these clients are reluctant to change their pet to a therapeutic renal diet due to perceptions about quality from large manufacturers, and the perception that quality of a product can be inferred from the ingredient declaration (and that pet food ingredients are what they imagine them to be based on ingredient names). These clients may be interested in instead feeding a home-prepared diet. If an appropriate balanced diet is formulated (with all of the above considerations in mind), this can be appropriate, and allows for minute adjustment as the cat's needs change over time, though many clients find it more difficult to transition their cat from commercial diets to home-prepared diets than from one commercial diet to another.

Commercial maintenance diets

In order to meet Association of American Feed Control Officials (AAFCO) profiles for maintenance of cats, the diet must provide phosphorus at a concentration higher than that recommended for cats with any stage of CKD[6]. This option may provide a more ideal protein intake, especially in stage 2 for low-energy-requirement cats, but sacrifices the benefits of phosphorus restriction, which are rarely argued. This could be mitigated to some degree, especially in earlier stages with phosphorus binders, but at some point, additional steps are needed to achieve more stringent phosphorus restriction.

Follow up

The author considers this the most crucial of any feeding plan, but also the most frequently neglected. Particularly with respect to the subject of this discussion, ensuring that the patient is:

1. Consuming the appropriate amount of calories to:
    a. Maintain their weight
    b. Deliver their protein requirement (failure here is likely the reason for many cats losing LBM on therapeutic renal diets)
2. Maintaining weight and LBM
3. Stable vs progressing with respect to stage of CKD

Adjustments may be required based on all of the above points; in which case, the above process should be repeated with the inclusion of the new data gained at follow up.

Feeding tubes

The author agrees that proactive feeding tube placement is incredibly useful in long-term management of CKD in cats, as this facilitates delivery of an appropriate diet in the face of inappetence (which should be fully and appropriately managed medically; concurrent disease is frequent in this patient population). Discussion of this option should occur early in the management of CKD (long before it is ever needed) so that the client can consider it when not in crisis. Presenting it as a therapeutic tool for managing disease and clarifying that it is not a means of prolonging poor quality of life is critical.

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5th WORLD FELINE VETERINARY CONFERENCE

Complex Disease Management

Exploring Feline Comorbidities

Oct. 31 – Nov. 3, 2019
Hilton San Francisco
Union Square
San Francisco, CA

SATURDAY, NOVEMBER 2, 2019

TIME	SESSION TITLE	SPEAKER	ROOM	SPONSOR/ PARTNER
6:15 - 7:15 am	Early Riser Yoga Class*		Franciscan C&D	
7:30 - 8:30 am	Breakfast		Exhibit Hall	
8:00 - 8:20 am	*Oral Abstract Session:* Pharmacokinetics of Single Dose Gabapentin for Stress Relief in Normal Cats	Dr. Jessica Quimby	Continental Ballroom 1-4	
8:00 - 8:20 am	*Oral Abstract Session:* Keep the Cat: A Novel Solution for Managing Cat Allergens	Mr. Ebenezer Satyaraj	Continental Ballroom 5-6	
8:00 - 8:20 am	*Oral Abstract Session:* Risk Factors for Welfare Behaviors of Concern in Owned Cats	Dr. Mikel Delgado	Continental Ballroom 7	
8:00 - 8:20 am	*Oral Abstract Session:* Evaluation of Mirtazapine Transdermal Ointment in Cats	Dr. Beasley Mason	Imperial Ballroom A	
8:30 - 9:20 am	CKD & Chronic Enteropathy: Clinical Implications of Gut-Renal Syndrome	Dr. Jessica Quimby	Continental Ballroom 1-4	KindredBio, RENAL
	Cardiomyopathy & Thromboembolic Disease	Drs. Ronald Li & Joshua Stern	Continental Ballroom 5-6	
	Technician/Nurse: Veterinary Technician's Role in the Feline Healthy Wellness Visit	Ms. Rachel Poulin	Continental Ballroom 7	zoetis
9:25 - 10:15 am	Cardio-Renal Syndrome	Drs. Jessica Quimby & Joshua Stern	Continental Ballroom 1-4	
	Diagnosis of Comorbidities on a Budget: Practical Diagnostic Options Can Help	Dr. Elizabeth Colleran	Continental Ballroom 5-6	IDEXX
	Technician/Nurse: Diabetes & the Role of the Technician in Disease Management	Ms. Rachel Poulin	Continental Ballroom 7	zoetis
10:15 - 11:00 am	Networking Refreshment Break		Exhibit Hall	
10:25 - 10:50 am	AAFP Membership Meeting		Imperial Ballroom A	
11:00 - 11:50 am	Hyperthyroidism & CKD: Now What?	Dr. Jessica Quimby	Continental Ballroom 1-4	KindredBio, RENAL
	Heart Disease & Respiratory Disease in the Cat	Drs. Ronald Li & Joshua Stern	Continental Ballroom 5-6	
	Technician/Nurse: Fluid Therapy	Ms. Ann Wortinger	Continental Ballroom 7	NAVTA
11:55 - 12:45 pm	The Role of Coinfections in Select Feline Clinical Disease Syndromes	Dr. Michael Lappin	Continental Ballroom 1-4	Pro Plan Veterinary Diets, RENAL
	Hypertrophic Cardiomyopathy & Co-Managing Hypertension or Hyperthyroidism	Dr. Joshua Stern	Continental Ballroom 5-6	
	Technician/Nurse: Nutritional Management of Patients With Vomiting & Diarrhea	Ms. Ann Wortinger	Continental Ballroom 7	NAVTA
12:45 - 2:10 pm	Lunch		Exhibit Hall	
1:00 - 2:00 pm	*Lunch & Learn #1:** Weight Loss in CKD: Is it the Protein or the Calories?	Dr. Angela Rollins	Imperial Ballroom A	KindredBio
1:00 - 2:00 pm	*Lunch & Learn #2:** It's so HARD! Feline Heartworm Case Management & Diagnostic Updates	Dr. Byron Blagburn	Imperial Ballroom B	MERCK Animal Health
1:00 - 2:00 pm	*Lunch & Learn #3:** Controlled Substances 101: How & Why You Must Comply!	Ms. Jan Woods	Yosemite	zoetis
1:30 - 2:00 pm	ABVP: Is it for Me?		Continental Ballroom 1-4	ABVP
2:10 - 3:00 pm	Feeding Senior Cats for Life-Managing Common Concurrent Needs	Dr. Julie Churchill	Continental Ballroom 1-4	Pro Plan Veterinary Diets
	Layers of Complexity: The Feline Imperative for Integrating Pharma & Non-Pharma	Dr. Bonnie Wright	Continental Ballroom 5-6	zoetis, IVAPM
	Technician/Nurse: Refeeding Syndrome: Does it Really Exist?	Ms. Ann Wortinger	Continental Ballroom 7	NAVTA
3:05 - 3:55 pm	Feeding Outside the Box: Nutritional Triage to Manage Comorbidities	Dr. Julie Churchill	Continental Ballroom 1-4	Pro Plan Veterinary Diets
	Managing the Peri-Operative Cat With Renal Disease from Start to Finish	Dr. Bonnie Wright	Continental Ballroom 5-6	zoetis, IVAPM
	Technician/Nurse: Counseling Clients in Crisis	Ms. Ann Wortinger	Continental Ballroom 7	NAVTA
4:00 - 4:45 pm	*Forum:* Cat Friendly Practice® FAQs		Continental Ballroom 7	Cat Friendly Practice
4:00 - 6:30 pm	Free Time			
6:30 - 10:30 pm	An Evening at the Exploratorium Offsite Event**			Elanco

*Separate Registration Required. No fees associated.

**Separate Registration Required. Additional fees apply.

Setting the Stage: Managing CKD

Jessica Quimby, DVM, PhD, DACVIM

Introduction

Establishing a solid relationship with the pet owner and tailoring recommended therapies to each individual case is an important part of successful management of feline chronic kidney disease (CKD). The treatment plan will fail if the owner does not understand why the medication is important, if they cannot administer it to the cat, and if follow-up visits and phone calls are not made to troubleshoot medication administration. It may be necessary to prioritize medications based on their medical necessity, the likely benefit to the patient, and the owner's ability to give the medication in order to balance quality of life with medical intervention. The level of evidence available to support the clinical efficacy of the treatment should therefore be considered when determining medication priority.

Nutrition and Diet in CKD

Several studies have documented the therapeutic value of specially formulated diet in the management of CKD (Grade 1), including amelioration of renal secondary hyperparathyroidism, decreased incidence of uremic crisis and increased survival.[1-3] Renal diet has also recently been demonstrated to decrease fibroblast growth factor 23 (FGF-23) levels, a marker that is positively correlated with disease stage, and is thought to be a mediator of renal secondary hyperparathyroidism.[1] These diets typically contain conservative amounts of high quality protein, adequate non-protein calories, and are restricted in phosphorus. The failure of the patient to eat the diet negates the benefit of dietary management, and therefore a key therapeutic target for these patients is the maintenance of appetite and food intake. Poor body condition is associated with a poorer prognosis in cats with CKD.[4] Additionally, poor appetite is perceived by owners as a significant quality of life concern and anorexia in companion animals can cause emotional distress to owners.[5] Cats with CKD often suffer from poor appetite, and although renal diets contain adequate dietary protein, the patient will be protein deficient if not eating its caloric requirement. Therefore management of long term dysrexia is important. Addressing complications of decreased kidney function (hydration, hypokalemia, anemia, etc.) that have the potential to affect appetite is important. If cats cannot be enticed to eat an appropriate amount of renal diet, then complete nutrition needs to be obtained via other sources.

Dysrexia

Nutritional Assessment

Clinical signs of nausea, vomiting and dysrexia are common in feline patients with chronic kidney disease (CKD).Serial evaluations of nutritional status are a key part of CKD patient management and a nutritional plan should be performed for every patient. Awareness of these parameters and tools for assessment have been made available by the WSAVA global nutritional initiative. http://www.wsava.org/nutrition-toolkit. A nutritional assessment should include body weight, body condition score, muscle mass score, adequacy of caloric intake (including open ended questions about how the pet is eating), and a complete dietary history (including pet food, treats, supplements and items used to give medications). Assessment of muscle mass is particularly important in CKD patients as it can have a profound effect on serum creatinine and affect the interpretation of the severity of disease, as well as have notable implications for the nutritional status of the patient.

Etiology of Dysrexia

The etiology of dysrexia in CKD is typically attributed to uremic effects on the intestinal tract, such as hyperacidity, uremic gastritis and ulceration but our understanding of this pathophysiology to cats is incomplete. Although cats with CKD have been shown to have elevated concentrations of gastrin that increase with the severity of kidney disease, [6] more recent information demonstrates this is likely not related to gastric pathology or hyperacidity. In a study evaluating the type and prevalence of histopathologic lesions in the stomach of cats with CKD, gastric fibrosis and mineralization were the main changes found rather than the uremic gastropathy lesions previously described in dogs and humans (uremic gastritis, ulceration, vascular injury, edema).[7] A recent study provided evidence that CKD cats may in fact not be hyperacidic.[8] However, if used, studies of the effect of omeprazole on the gastric pH in normal cats indicates that it is superior to famotidine in its ability to inhibit acid production at 1 mg/kg q12h (Grade 1).[9]

Uremic Toxins and Appetite Dysregulation

Uremic toxins are sensed by the chemoreceptor trigger zone (CRTZ) of the area postrema in the brain, which subsequently stimulates emesis by the vomiting center. Therefore the use of medications that target receptors in the CRTZ (i.e. $5HT_3$ and NK_1) may be useful in the management of nutrition in CKD. In addition to build up of uremic toxins, the basic pathophysiology of appetite regulation may be significantly abnormal in cats with CKD. Appetite regulation is comprised of orexigenic substances that activate the hunger center (i.e. ghrelin) and anorexigenic substances that activate the satiety center of the brain (i.e. leptin, cholecystokinin, obestatin, des-acyl ghrelin).[10] In

humans, CKD is associated with an increased accumulation of anorexigenic substances secondary to decreased glomerular filtration rate without a concomitant increase in orexigenic substances such as ghrelin. Additionally anorexigenic substances have been demonstrated to be significantly higher in CKD patients with poor body condition than those with normal body condition.[10]

Anti-nausea/Anti-emetic Therapy
Several anti-emetic therapies are available and include maropitant, ondansetron and dolasetron. Ondansetron has been documented to be effective in human patients suffering from uremia.[11] However pharmacokinetic studies in cats have demonstrated that oral bioavailability of ondansetron (0.5 mg/kg) is poor in cats (~35%) and the half -life is very short (approximately 1 hour) making it a q 6-8h medication.[12] Subcutaneous ondansetron has a slightly longer half-life of 3 hours. In addition to its appetite-stimulating properties, mirtazapine demonstrates anti-nausea properties as it acts at the $5HT_3$ receptor similarly to ondansetron and dolasetron (Grade 4).[13,14] A recent study assessed the efficacy of maropitant for management of chronic vomiting associated with feline CKD (Grade 1). When given orally (4 mg q24h) for two weeks, Cerenia was demonstrated to palliate vomiting associated with CKD.[15] A pharmacokinetic and toxicity study in cats indicated that longer-term usage appears safe.[16]

Appetite Stimulant Therapy
Mirtazapine has become commonly used as an appetite stimulant in cats and a placebo-controlled, double-blinded crossover clinical trial was performed to evaluate the effects of mirtazapine on body weight, appetite, and vomiting in cats with CKD (Grade 1).[14] Mirtazapine is an effective appetite stimulant in cats with CKD and resulted in significantly increased appetite and weight. Mirtazapine also appears to have anti-emetic properties and resulted in significantly decreased vomiting in cats with CKD. Hyperactivity and vocalization are side effects and are generally dose-dependent; smaller, more frequent doses are recommended (1.87 mg orally q48h) (Grade 1).

Mirtazapine is also amenable to transdermal administration and has been demonstrated to achieve both appropriate serum levels, appetite stimulation and weight gain in cats.[17-19] Transdermal administration is an extremely attractive method for administering medications, however not all drugs are amenable to transdermal application and each requires testing for appropriate drug exposure and clinic efficacy. The appetite effect of transdermal preparations is much more subtle than oral mirtazapine due to a flatter drug concentration curve, [18,19] a phenomenon that also results in fewer side effects. Clinical studies of transdermal mirtazapine (compounded Lipoderm) in cats with CKD are underway.[20] Transdermal mirtazapine ointment has also recently become FDA approved for the management of unintended weight loss (Mirataz®) and efficacy has been documented in pharmacokinetic and pharmacodynamics studies.[17,18]

Future availability of the ghrelin agonist capromorelin may also provide additional opportunities to address appetite in cats with CKD by targeting the pathophysiology of appetite regulation. In both human and rodent studies administration of ghrelin has resulted in increased appetite and energy intake in patients with CKD. In a recent abstract, administration of capromorelin resulted in increased food intake and weight in laboratory cats.[21]

Systemic Hypertension
Systemic hypertension appears to be common in cats with CKD (20-65%), but the exact pathophysiologic relationship is unknown. Systemic hypertension can have other deleterious effects such as retinal hemorrhage and detachment, neurologic and cardiac impairment. Elderly cats, particularly those with renal impairment should be routinely screened. Unless blood pressure is >200 mm Hg and/or evidence of target organ damage is seen, such as retinal hemorrhage, blood pressure should be rechecked to rule out white coat hypertension. Azotemic cats with blood pressure persistently >160 mm Hg are candidates for treatment. Amlodipine is documented to be an effective treatment for hypertension in the cat and is currently the most common medication prescribed at 0.625-1.25 mg/cat q24h (Grade 2).[22,23] Telmisartan is also an effective anti-hypertensive medication in cats and has recently become approved for this indication in cats (United States: 1.5 mg/kg q 12h for 14 days, then 2 mg/kg q 24h for hypertension) as well as an anti-proteinuric (UK and Europe: 1 mg/kg daily).[24-26] For all anti-hypertensive therapy, blood pressure should be recheck within 7-10 days after initiating treatment.

Proteinuria
Cats most commonly develop proteinuria secondary to their CKD, particularly in later stage disease, due to tubular dysfunction and/or glomerulosclerosis, as opposed to developing true protein-losing nephropathy (PLN) like dogs. Proteinuria is associated with poorer prognosis in cats.[27] Several studies looked at efficacy of ACE inhibitors (benazepril) for treatment of proteinuria in cats and it was documented that benazepril decreases proteinuria in cats with CKD (Grade 1), but results were only suggestive of long-term benefit, not conclusive.[28] Nonetheless it is generally recommended that cats with *renal* proteinuria with a urine protein creatinine ratio > 0.4 on at least two repeated measurements should be treated (0.25-0.5 mg/kg benazepril orally q24h). Careful monitoring is required because ACE inhibitors may result in decreased GFR and subsequent worsening of renal function. Kidney values,

electrolytes and blood pressure should be rechecked within one week of initiating therapy. Because of the negative effect on GFR, ACE inhibitors are not recommended for late state patients or those in uremic crisis. Telmisartan is an angiotensin receptor blocker (licensed in Europe for treatment of proteinuria/hypertension and in the US for hypertension in cats) that has been found to be more effective than benazepril for treating proteinuria (Grade 1).[24] In the uncommon instance that a cat has primary glomerular disease, a recent abstract indicates that a significant portion of these may be immune-mediated, and immunosuppressive therapy may be warranted.

Hydration
Although it has not been systematically assessed in a clinical trial, adequately maintaining hydration by giving subcutaneous fluids anecdotally appears to substantially help quality of life, improve appetite and activity (Grade 4). It can be a very helpful tool for owners in management of disease, but may not be necessary for every patient. The best candidates for SQ fluid therapy (75-150 ml SQ every 1-3 days) are those cats that appear to gain clinical benefit from management of hydration, are prone to secondary complications of chronic dehydration such as constipation, and do not suffer quality of life concerns from the procedure. If possible, supplementation with free water (orally or with a feeding tube) is preferred to avoid the sodium load that comes with the electrolyte solutions available for subcutaneous use. Feeding canned food instead of dry, or adding water to food is another way to potentially increased water consumption. Paying special attention to water sources in the house – fresh, accessible, water fountains etc., is also key.

Anemia
The kidney is responsible for producing the hormone erythropoietin which stimulates the bone marrow to produce red blood cells. As kidney disease progresses, the hormone levels decrease and anemia can result. Chronic low-grade gastrointestinal hemorrhage may also contribute to anemia and iron deficiency may be noted. The deficient hormone can be supplemented with artificial products such as recombinant human erythropoietin Darbepoetin alpha. Darbepoetin is a longer-acting form of erythropoietin and is thought to have less association with anti- erythropoietin antibodies than the previously used Epogen (Grade 3).[29] Darbepoetin is currently the product of choice, but expense can limit its use for some owners. Iron supplementation is recommended when therapy is initiated as a relative iron deficiency has been shown to be present in CKD cats (iron dextran 50 mg/cat IM, Grade 4 for dose).[30] Recommended starting dose for Darbepoetin is 0.5-1 mcg/kg subcutaneously once weekly until the low end of the normal PCV range is reached, then injections are decreased to once every 2-3 weeks as needed to maintain PCV (Grade 3).

Hypokalemia
Inadequate dietary intake, increased urinary loss and activation of the renin-angiotensin-aldosterone system are all thought to contribute to hypokalemia. Hypokalemia is associated with development and worsening of CKD in humans and appears to exacerbate damage to tubular epithelial cells.[31] Serum potassium levels are not representative of systemic tissue potassium levels and cats with low normal serum potassium may actually be systemically depleted.[32] Potassium is vital for normal muscle function, GI motility and supplementation has been demonstrated to correct hypokalemic myopathy (Grade 3).[33] Some clinicians recommend supplementation even when serum potassium is in the low normal range[11], with a goal of maintaining serum potassium levels above 4 mg/dL, but the effect on the progression of CKD has not been evaluated.

Hyperphosphatemia
The kidneys are the main route of phosphorus excretion and as kidney function declines, hyperphosphatemia develops. Hyperphosphatemia is detrimental because it contributes to renal secondary hyperparathyroidism, tissue mineralization and progression of CKD. Hyperphosphatemia has been identified as a predictor of progression in feline CKD, thus controlling phosphorus intake through diet and phosphate binders is important part of CKD management (Grade 2).[27,34] If a renal diet is initiated and phosphorus is still elevated after 4-6 weeks, then a phosphate binder is recommended with the goal of keeping serum phosphorus in the low normal range.[26] These medications bind the phosphorus in the food and make it less bioavailable so it is critical that the owners understand the medication should be given with each meal. Several different phosphate binders are available including aluminum hydroxide (30-100 mg/kg/day), calcium carbonate (90-150 mg/kg/day), and lanthanum carbonate (30 mg/kg/day),[26] As phosphate binders are dosed to effect – with a target phosphorus range for each IRIS stage as outlined by the IRIS recommendations for CKD therapy (www.iris-kidney.com) – these ranges are just a starting point and therapy is titrated to effect. However the main problem with administration is palatability and this often limits the amount that can be reasonably administered. Serum calcium should be monitored when calcium-containing phosphate binders are used and an alternative binder should be used if hypercalcemia develops.

Calcitriol
Renal production of calcitriol, the active form of Vitamin D, is decreased in CKD and hyperphosphatemia further inhibits its synthesis. Calcitriol is an important inhibitor of parathyroid hormone and low levels leads to renal

secondary hyperparathyroidism which has multiple deleterious consequences. In dogs and people, use of calcitriol has been shown to be beneficial (Grade 1 in dogs),[35] but a study performed in cats was not supportive.[36] Current guidelines for management of feline CKD do not support the use of calcitriol.[37] Nonetheless, controversy remains and despite lack of evidence some clinicians recommend supplementation at 2 ng/kg orally daily on an empty stomach (Grade 4). Careful monitoring of ionized calcium and PTH levels is *required* as hypercalcemia and mineralization can result from over-supplementation, particularly if given with food. If hypercalcemia results, the medication should be discontinued, although some advocate that every other day administration will correct the hypercalcemia.[35]

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Cardio-Renal Syndrome

Jessica Quimby, DVM, PhD, DACVIM & Joshua Stern, DVM, PhD, DACVIM (Cardiology)

Introduction

Renal disease and cardiac disease are common conditions in feline patients, and represent a complex management challenge. Cardio-Renal syndrome is a term that was implemented in human medicine to describe the complex pathophysiologic interactions between the renal and cardiovascular systems. The importance of the bidirectional influence of these two organ systems is highlighted by evidence that outcomes in human patients with both conditions are worse than for those patients with either condition alone. In veterinary medicine we have only just begun to understand the interplay between these systems and their implications in both health and disease. The schema of classification in human medicine has been adapted for veterinary medicine by a team of cardiologists and nephrologist and helps to define what we current know about cardiorenal syndrome in cats.[1,2] Starting to understand the complex processes at play will help us better understand how best to balance cardiac and renal disease. Key to this process is very simply that awareness and early recognition are important to improve patient outcomes.

Brief overview of Cardio-Renal Definitions

Human Classification	Vet Classification	Brief Definition	Conditions
Type 1: Acute Cardiorenal syndrome	$CvRD_H$ unstable	Acute impairment of the cardiac function leading to acute kidney injury (AKI)	Acute heart failure Cardiogenic shock
Type 2: Chronic Cardiorenal syndrome	$CvRD_H$ stable	Chronic cardiovascular disease causing progressive chronic kidney disease (CKD)	Chronic heart failure "Congestive nephropathy"
Type 3: Acute Renocardiac syndrome	$CvRD_K$ unstable	Acute primary worsening of kidney function that leads to cardiac dysfunction	AKI Hyperkalemia, uremia
Type 4: Chronic Renocardiac syndrome	$CvRD_K$ stable	Primary CKD that contributes to cardiac dysfunction	Chronic glomerular disease, anemia, systemic hypertension
Type 5: Secondary Cardiorenal syndrome	$CvRD_O$	Cardiac and renal dysfunction secondary to an acute or chronic systemic condition	Hyperthyroidism Pancreatitis Sepsis

Abbreviations: CvRD: cardiovascular-renal axis disorders. (*From Cowgill and Orvalho, VCNA 2017*)[1]

Cardio-Renal Syndrome in Veterinary Medicine

$CvRD_h$: Renal disease/dysfunction emanating from cardiovascular system

One of the most common clinical manifestations of $CvRD_h$ in cats is the effect that medications (ACE inhibiters and diuretics) used to manage heart disease have on the kidney. These alone or in conjunction with low cardiac output and hypotension can lead to decreased renal perfusion and potential subsequent azotemia and AKI. In its mildest manifestation, this may typically present as dehydration and mild, presumably pre-renal, azotemia. But the degree to which subtle kidney injury is occurring with chronic dehydration is unknown as biomarkers for cats are not well developed and the borderline between pre-renal azotemia and renal azotemia is not understood. Elevation in creatinine may result only after significant injury has occurred. Additionally, in the event of uremic crisis, cardiac medications may further enhance renal insult.

In addition to more clinically apparent and emergent outcomes like AKI, chronic subclinical dehydration could also have negative consequences for the kidney. Dehydration may result in vasopressin release, RAAS activation and poor perfusion all of which could have detrimental effects on the kidney. Effects of vasopressin include efferent arteriolar constriction resulting in increased intraglomerular hypertension, and potentially the development of proteinuria and hypertension.[3] Furthermore vasopressin has non-hemodynamic effects with negative consequences such as mesangial cell proliferation and hypertrophy, production of collagen and fibronectin, which may contribute to the development of glomerulosclerosis.[3] RAAS is poorly understood in cats (both normal and diseased). Preliminary evidence suggests RAAS response in hypertension and CKD may differ in cats in comparison to other species, [4] but likely heart disease itself exacerbates RAAS activation in renal patients via a variety of mechanisms.

Volume overload in CHF can have detrimental effects at the level of the kidney parenchyma referred to as "congestive nephropathy" which occurs as a result of renal venous congestion. Although this has not been studied specifically in feline pathology, in mouse models fluid overload results in interstitial edema, increased renal venous pressure and renal congestion which have negative effects on GFR.[5,6] In CKD patients on dialysis fluid overload is associated with a poorer prognosis.[7] In acute kidney injury fluid overload is associated with negative outcomes in humans such as poorer renal recovery, increased need for dialysis and higher mortality rates.[8]

Thromboembolic disease associated with heart disease may have the potential to have downstream effects on the kidney. Some evidence for this exists as one retrospective study that examined concurrent conditions in cats with renal infarcts diagnosed on ultrasound or necropsy, cats with renal infarcts were 4.5 times more likely to have HCM than cats without renal infarcts, and 8 times more likely to have distal aortic thromboembolism than cats without renal infarcts.[9] This link prompted authors to recommend cats with renal infarcts should be screened for occult cardiomyopathy.

$CvRD_k$: Cardiovascular disease/dysfunction secondary to renal disease

Cats with evidence of cardiac disease, in particular echocardiographic changes consistent with left ventricular hypertrophy, are often oversimplified into the umbrella category of hypertrophic cardiomyopathy. Given that HCM has a reported incidence of roughly 1 in 7 adult cats and perhaps and approximately 1 in 3 senior cats, it is important to recognize that there are several systemic conditions result in similar disease features and outcomes of HCM. Far and away the most important systemic condition afflicting cats and resulting in cardiovascular change is systemic hypertension. Systemic hypertension is most commonly secondary to kidney disease in the cat and leads to downstream cardiovascular effects attributable to a pressure overload physiology. Cardiac end-organ damage from systemic hypertension involves a hypertrophic response in the left ventricle which is indistinguishable from that of HCM. The elastic great vessels may dilate and be seen as aortic dilation on echocardiography or undulation of the thoracic aorta on thoracic radiographs. With conformational change to the LV chamber from hypertrophy, dilation of the aorta, and elevated diastolic pressure within the aorta, the aortic valve may become incompetent and result in clinically relevant aortic insufficiency and rarely volume overload secondary to this phenomenon. Additional organ effects of systemic hypertension include the vasculopathy and retinopathy.

Concomitant kidney disease and cardiac disease represents a delicate balancing act for the clinician. While some kidney disease can be the direct cause of cardiovascular signs, it is perhaps more common to see kidney disease exacerbate some pre-existing cardiac condition. For example, one significant concern in patients with both cardiac and kidney disease is the effect of additional vascular volume on the heart. Kidney injury can result in volume overload which is a major challenge for cats with underlying cardiac disease to manage. Cats with subclinical cardiac disease have their disease unmasked by the effects of volume overload quite commonly. Cats with subclinical or overt HCM have significant diastolic dysfunction that limits their ability to handle increased fluid volume. This increased fluid volume may be the result of ongoing renal disease or iatrogenic in the case of patients being treated for their renal disease with intravenous or subcutaneous fluid administration. It is relatively common in the author's practice to see patients being treated for acute kidney injury or chronic renal disease that end up with congestive heart failure during treatment with fluid therapy.

As previously mentioned, RAAS activation happens in response to many conditions, including both cardiac and renal disease. The impact of RAAS activation on the cardiovascular system is similar to the concerns of volume overload noted above. In the setting of a non-compliant, ventricle, this drive for sodium and water retention could lead to volume overload and subsequent congestive heart failure, particularly in feline patients with underlying, subclinical myocardial disease like HCM.

Volume depletion may also impact cardiac performance and alter cardiac output. Uremic feline patients may be dramatically dehydrated due to anorexia and/or vomiting. Thus they often have reduced vascular volume that can limit cardiac output and further exacerbate poor organ and tissue perfusion. Fluid therapy is indicated in these patients but should be done cautiously to ensure that they can handle the rate and volume provided.

Electrolyte disturbances, namely hypokalemia or hyperkalemia, secondary to renal disease can also have significant impact on the heart, namely cardiac electrophysiology. Feline cardiomyocytes are sensitive to potassium changes and can respond in a variety of ways from supraventricular and ventricular arrhythmias to AV blocks and bradycardia. Monitoring of electrolytes in patients with kidney disease is important and significant derangements in potassium should prompt ECG evaluation. In the author's experience these derangements infrequently warrant antiarrhythmic drugs and the majority of feline patients respond to both judicious fluid therapy and supplementation when needed.

The anemia of chronic kidney disease may impact cardiovascular performance and assessment of heart size for clinicians. Cats with severe anemia have measurable chamber dilation on echocardiography that may be confused with myocardial disease. The impact of reduced oxygen carrying capacity of the blood may lead to additional stress

on the myocardium which could be particularly relevant in patients with underlying subclinical HCM where myocardial oxygenation may already be impaired.

Finally, the impact of kidney function on drug clearance must be considered. Drugs with a narrow therapeutic spectrum of safety that rely on renal clearance should be used cautiously in cats with known renal impairment. For example, treating a feline patient that has atrial fibrillation with digoxin in the face of renal impairment is extremely dangerous and can lead to toxic drug levels. Evaluating basic renal parameters such as BUN and Creatinine are an essential part of managing feline cardiac disease, in part to ensure that drugs cleared by the kidney are dosed and managed appropriately.

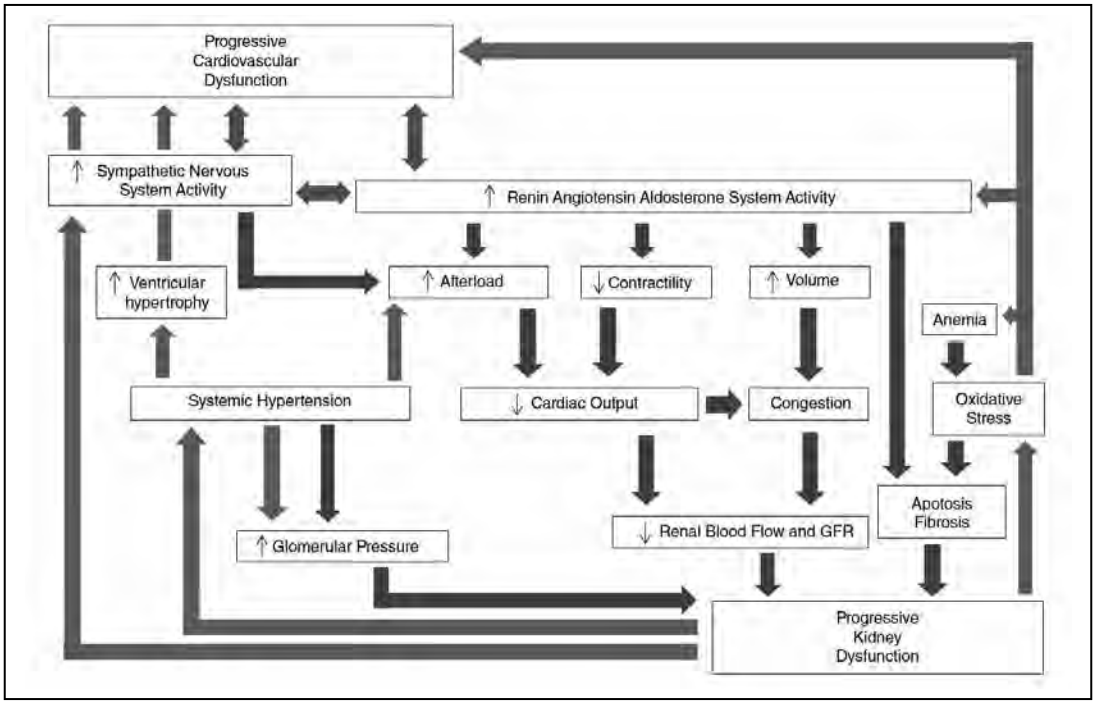

Figure 1: Proposed mechanisms involved in the interactions between renal and cardiovascular systems. Blue arrows indicate pathways by which cardiac dysfunction may lead to kidney dysfunction. Conversely red arrows indicate pathways by which kidney dysfunction may lead to cardiac dysfunction. (*From the BSAVA consensus statement*)[2]

$CvRD_0$: Concurrent impairment of both systems caused by other disease processes
In humans, several systemic common disease processes affect both the cardiovascular and renal organ systems, including diabetes mellitus and sepsis. Fortunately for feline patients, diabetes has not been proved to instigate CKD and sepsis is rare. Other uncommon causes of systemic impairment in feline patients would be diseases such as acromegaly, infectious disease leading to endocarditis/myocarditis, septic or neoplastic emboli, and amyloidosis. Severe necrotizing pancreatitis likely has the ability to tip off multi-organ failure. However, hyperthyroidism is likely the most common feline disease that has effects on both the heart and kidney and should be investigated in any cat with clinical signs consistent with elevated T4 and any cat >6yrs that has evidence of cardiac hypertrophy. The role of T4 and cardiac disease in feline patients is reviewed in a separate lecture and proceedings from Dr. Stern.

What do we do about feline Cardio-Renal syndrome?
Identify patients who have both diseases
The very first step to managing a patient with concurrent illness is to identify both diseases exist as knowledge is power and awareness should result in heightened scrutiny that will catch problems before they are too advanced. All patients with diagnosed cardiac disease, primarily HCM in the cat, should be screened for renal impairment, and concomicant conditions such as systemic hypertension. Treatments for underlying renal disease and cardiac disease may exacerbate clinical or bring to light subclinical disease of the other organ system. However diagnosis can be challenging as there are multitude of conditions associated with CKD that might result in a heart murmur (hypertension, anemia, dehydration) and of course all cats with heart disease do not have a murmur. Conversely diagnosing cats with CKD who are already undergoing therapy for heart disease can be challenging as medications may result in dilute urine and mild dehydration. Echocardiogram should be pursued in CKD cats with suspicion of heart disease, particularly if fluid therapy is warranted. However hypertension can confound determination of whether

intrinsic cardiac disease is present. In addition to the regular reevaluations for managing systemic hypertension, the author's practice recommends reevaluation of echocardiography after 9-12months of adequate BP control. Recent research has concentrated on the development of biomarkers to facilitate early detection of insult to heart or kidney to improve early detection.[1] However development of biomarkers specific to cats are needed to further advance these diagnostic capabilities.

Table 2: Therapeutic approach to a cat with cardiorenal syndrome

1. Recognize and anticipate CvRD	- Record baseline BUN/Cr/USG/UPC ratio/SBP - Monitor for serial Cr increases over time
2. Optimize heart failure therapy	- Use lowest effective dose of furosemide - Consider dual-diuretic therapy - Consider torsemide if diuretic resistance - Use ACE inhibitors - Use other cardiac drugs directed at primary disease - Perform thoracocentesis/abdominocentesis as needed
3. Evaluate and monitor renal function	- CBC/serum chemistry profile/urinalysis ± UPC ratio - Repeat every 1–3 months or when changing treatment plan - Culture urine if indicated - Ultrasound abdomen
4. Control hypertension	- Assess systolic blood pressure (SBP) - Treat when SBP ≥160 mm Hg - Use amlodipine and/or telmisartan
5. Avoid hypotension	- If SBP <100 mm Hg - Reassess potentially hypotensive drugs - Consider positive inotropes
6. Improve renal function/optimize renal therapy	- Supplement with omega-3 PUFA - Feed renal diet if ≥ IRIS stage 2 - Ensure adequate calories are ingested to optimize BCS/MCS - Consider phosphate binders - Supplement with potassium - Control gastrointestinal signs (anti-emetic, appetite stimulants) - Address dehydration (consider sodium content of fluid in patients with advanced cardiac disease)
7. Improve cardiac output	- Consider positive inotropes - Treat hypertension if present
8. Correct anemia of CKD	- When HT <20-25% - Darbepoetin administration - Supplement iron if indicated
9. Review and modify drug dosages	- Extend dosage interval of renally excreted drugs - Check for drug interactions

Modified from: Belanger MC**.** Heart failure and chronic kidney disease. In: Little, S, ed. *The Cat: Clinical Medicine and Management*. Elsevier, 2nd edition.

Prognosis

In general the prognosis for patients with cardiorenal syndrome is guarded, particularly when stage of disease is advanced. Early detection, careful monitoring, titration of therapies and a dedicated, observant care are helpful to strive for the best outcome.

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Hyperthyroidism & CKD: Now What?

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Introduction

Hyperthyroidism and chronic kidney disease (CKD) are both very common conditions in the elderly cat and therefore concurrent illness is not uncommon. Hyperthyroidism occurs in 1.5-11.4% of cats worldwide and approximately 10% of cats over the age of 10 years in the USA.[1] Chronic kidney disease occurs in 30-80% of elderly cats and increases in frequency with age.[2,3] In one study, 22.8% of cats had concurrent hyperthyroidism and CKD.[4] Therefore understanding the implications of concurrent disease on diagnostics, management and monitoring of therapy is crucial to the safest and most effective outcome.

Effects of hyperthyroidism

Clinical signs of hyperthyroidism are familiar to the practitioner and typically include weight loss with concurrent polyphagia, PUPD, increased vocalization, agitation and increased activity, vomiting and diarrhea, tachypnea, tachycardia, and poor hair coat. However it is also important to consider the pathophysiologic effects of hyperthyroidism particularly as it relates to the kidney. Hyperthyroidism results in increased GFR as a result of increased cardiac output and renal perfusion leading to the classic "masking" of underlying CKD.[5] However it is important to realize that while renal function parameters appear improved, this hyper filtration may have deleterious effects including beta-adrenergic activity and activation of renin-angiotensin-aldosterone system and glomerular hypertension and hyperfiltration.[1,5-7] Glomerular hypertension and hyper filtration can lead to glomerular sclerosis and proteinuria, the latter of which subsequently increases proximal tubular workload and is a factor for progression in CKD.[6] Therefore not treating or maintaining a mild hyperthyroid state to "support" the kidney is not recommended.[1]

Considerations for disease diagnosis

Chronic kidney disease may complicate the diagnosis of hyperthyroidism by acting as a non-thyroidal illness and it may be challenging to determine if weight loss is because of CKD alone, or if another disease plays a role. Although traditionally it has been commented that cats in earlier stages of CKD do not demonstrate clinical signs such as weight loss (and that another disease should be suspected), a recent retrospective study assessing weight loss in CKD cats has shed doubt on this assumption as cats of all CKD stages were observed to lose weight.[8] Approximately 10% of hyperthyroid cats with have normal free T4 on initial evaluation.[9] Free T4 may not be helpful for diagnosis due to its sensitivity and therefore high rate of false positive results (20-33%) particularly with CKD and is best combined with other tests.[9] One study demonstrated TSH was reliably decreased in all cases of concurrent disease.[10] Nuclear scintigraphy or T3 suppression test are useful ancillary diagnostics.[9] It is important to interpret diagnostic tests in light of clinical findings as cats in which creatinine "improves" that have clinical signs of hyperthyroidism are suspect. Tests may be more powerful when performed in conjunction with each other.[10]

Determining the presence of underlying CKD concurrent to hyperthyroidism can be challenging. Decreases in creatinine with onset of hyperthyroidism may be the result of hyper filtration or also muscle mass loss. Muscle wasting is common in both hyperthyroidism and CKD. In a recent study significant numbers of hyperthyroid cats displayed muscle wasting: 38% had mild muscle wasting, 30% had moderate muscle wasting and 9% had severe muscle wasting.[11] Recent abstract data suggests that SDMA may therefore potentially be a useful test in assessing the presence of underlying CKD as it is less affected by muscle mass than creatinine. However, the effects of hyperthyroidism on SDMA are still being elucidated. It is important to realize that SDMA is not a substitute for a urinalysis including USG and urine sediment exam. A decreased urine specific gravity is a common early indicator of CKD in cats and trends over time should be monitored. A recent publication demonstrated that a USG > 1.035 was a useful tool for ruling out concurrent CKD.[12] Therefore obtaining a baseline urinalysis and continuing to monitor USG throughout therapy is a useful tool and available parameters are more powerful in conjunction with each other.

Therapeutic options

Practitioners are familiar with the standard therapies for hyperthyroidism including medical management, diet, radioactive iodine and surgery, however the utility of these therapies given concurrent or possible concurrent CKD should be considered. For CKD it is recommended that a less permanent therapy (medical management or diet) be the initial step in management to determine the response to disease and the degree of CKD that will be unmasked.[1] CKD supportive care therapies may need to be instituted or increased. If a more permanent therapy for hyperthyroidism is then elected, CKD supportive care therapies may need to be more aggressive.

The main advantage of medical management (methimazole) in CKD is more exact control over the outcome and the ability to reverse or discontinue therapy to prevent azotemic hypothyroidism. My personal approach to the cat with

concurrent disease is to start at a lower methimazole dose than normal, and gradually titrate up to the needed dose as opposed to the more common opposite approach which would result in a potentially precipitous drop in GFR and worsening of severity of CKD clinical signs. Disadvantages of course include administration, frequent monitoring for safety, and drug reactions. With CKD it is recommended to initiate medical management with methimazole at a low dose (1.25 mg BID) and slowly increase the dose to prevent a clinical decompensation. Iodine restricted diet is also a potential therapy in CKD with a demonstrated 82% efficacy with strict adherence to the diet (which may be an issue if appetite is picky with CKD). The base diet is relatively low in phosphorus compared to maintenance diets and was designed as a "geriatric" diet so would be appropriate for early CKD.

Radioactive iodine has become the treatment of choice for hyperthyroid cats due to its effective cure, low incidence of procedural side effects and ability to destroy cells wherever they may be located. However, the incidence of hypothyroidism post therapy is potentially significant (10-30%) and azotemic hypothyroidism in particular carries a worse prognosis.[13] If hypothyroidism is present, particularly in the face of azotemia, supplementation is recommended. Obviously this is not a popular turn of events if the original reason for performing radioactive iodine therapy was difficulty with oral medication. More recent data on using "low dose" radioactive iodine (2 mCi vs 4 mCi) has indicated that it is more ideal to titrate I 131 dose to the individual cat to decrease the incidence of hypothyroidism.[14] This would be particularly ideal in patients with CKD or suspected CKD.

Although effective, thyroidectomy is a less ideal option in cats with CKD or suspected CKD most obviously due to the need for anesthesia and hospitalization and its irreversible nature. If necessary due to the potential for carcinoma or the presence of cystic thyroid mass, stabilization with medical therapy before anesthesia is recommended. Cats with unilateral disease and no evidence of ectopia are thought to be the best candidates for thyroidectomy. Iatrogenic hypothyroidism can be a common concern with bilateral removal, necessitation supplementation in the azotemic patient.[13,15]

Client communication and monitoring post therapy

In order to boost compliance and owner engagement there are some key client communications to recommend in concurrent hyperthyroidism and CKD. Explaining the deleterious nature of the hyperthyroid state so that the owner understand why treatment is necessary as well as what to expect after initiation of therapy is key. The CKD hyperthyroid cat may look to the owner like it is clinical doing well, active and eating well, and after initiation of therapy may return to a "normal" geriatric CKD state of decreased activity and picky appetite. This must be separated from side effects of therapy (specific of methimazole) and increased supportive care may be necessary.

Additionally methimazole has a significant number of side effects for which regular monitoring is necessary including hepatopathy, gastrointestinal upset, bone marrow dyscrasias and facial pruritis. Appropriate monitoring includes total T4, CBC, chemistry for liver, kidney and electrolyes, USG and blood pressure as well as physical exam, nutritional assessment, body weight, body condition score and muscle mass score. If there is a significant concern for CKD these should be checked 2 weeks after dose initiation or change, and then every 1, 2-3 and 4-6 months as needed for the stage of CKD. Once again iatrogenic hypothyroidism has a deleterious effect and should be identified and a dose change made. The importance of monitoring is highlighted by the frequency with which issues occur which should be addressed. Azotemia develops in 15-51% of cats after initiation of therapy, 14-22% of cats are hypertensive at diagnosis and 24% develop hypertension, and 67% percent of responders in one survey reported adverse reactions to medical therapy.[16]

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CKD & Chronic Enteropathy: Clinical Implications of Gut-Renal Syndrome

Jessica Quimby, DVM, PhD, DACVIM

Introduction

Chronic enteropathy and CKD are common conditions in elderly cats, and when concurrent disease exists, it may complicate diagnosis and management of disease. At what point is weight loss attributed to CKD, or a concurrent condition such as chronic enteropathy (CE)? Furthermore, what is the effect of intestinal health on the kidney? In humans, a growing body of research supports the concept that there is significant connection between the gut and the kidney, and that both systems have important influences upon the other with potential significant clinical implications.

Conundrum of Diagnosis

The presence of concurrent CKD and chronic enteropathy in the feline patient may provide a challenge. Although traditionally it has been commented that cats in earlier stages of CKD do not demonstrate clinical signs such as weight loss (and that another disease should be suspected), a recent retrospective study assessing weight loss in CKD cats has shed doubt on this assumption as cats of all CKD stages were observed to have lost weight prior to as well as after diagnosis.[1] Once diagnosed with CKD, accurate IRIS staging may be difficult due to muscle mass loss from both conditions. Determining whether proteinuria is attributable to renal disease and merits treatment will also be challenging because systemic inflammation associated with CE may alter glomerular permeability and result in proteinuria.

Current Clinical and Therapeutic Implications of GI Disease

Chronic Enteropathy

There are a multitude of ways in which presence of CE may affect assessment or treatment of CKD. Cobalamin deficiency is common in older cats and definitely more common in older cats with CE so levels should be checked and supplementation implemented. The effect of hypocobalaminemia on anemia is understudied in cats, but is potentially a concern. Female cats with CKD have a higher incidence of UTI and diarrhea associated with CE may further exacerbate the development of UTI. Accurate assessment of phosphorus and calcium may be difficult as CE is associated with hypophosphatemia. After control of CE, phosphorus levels should be rechecked to see what further action is necessary. Additionally the effect of intestinal disease on drug absorption is unstudied for many of the medication we utilize. And most importantly concurrent disease has huge implications for nutrition as we spend a great deal of time fighting for caloric adequacy in CKD, and this will be further compromised by malabsorption of nutrients. As an inflammatory condition, CE likely also exacerbates the functional iron deficiency seen in CKD whereupon upregulation of hepcidin secondary to inflammation decreases the availability of iron.[2,3] This would likely increase the possibility of anemia associated with both diseases as well as the need for iron supplementation when darbepoetin is administered. Lastly what potential effect the dysbiosis associated with CE has on the kidney has not been studied.

Constipation

The prevalence of constipation associated with CKD has not been reported, however anecdotally this appears to be a common medical concern. Preliminary results of a survey study of fecal habits in cats suggest that defecation is less regular in CKD. The etiology of constipation associated with CKD is likely a dysfunction of water balance possibly combined with abnormal GI motility. As the kidney fails to provide appropriate urine concentrating ability and the patient fights with chronic subclinical dehydration, water is reabsorbed from the colon to compensate. Additionally hypokalemia and use of phosphate binders may also contribute to constipation.[4,5] Therapy for constipation may include correction of dehydration and electrolyte imbalance, diet, fiber, osmotic stool softeners or promotility agents such as Miralax or lactulose. In addition to clinical effects, constipation may have other negative consequences. Constipated human patients with CKD have higher levels of uremic toxins that patients with normal fecal scores, and conversely uremic toxins may have negative effects on gastrointestinal motility.[6,7] A rodent model of CKD demonstrated significant improvement in uremic toxins, creatinine and even kidney histopathology subsequent to a regimen of lactulose.[8]

The Gut-Renal Axis: Food for Thought

Microbiome and Gut-derived Uremic Toxins

The vast number of microorganisms that reside in the intestinal tract (the gut microbiome) play an important role in maintaining host health, and alteration of this microbiome has been associated with many illnesses in humans including CKD. The uremia associated with CKD has been shown to negatively impact the gut microbiome in humans and rats causing intestinal dysbiosis.[9,10] In humans and rats with CKD, these changes shift the microbiota to a less

diverse community that is more dominated by certain bacterial families.[9] Other instigators of intestinal dysbiosis in CKD patients include frequent use of antibiotics, dietary changes such as decreased fiber intake, and phosphate binders.[10-13]

The intestinal dysbiosis associated with CKD has also been shown to contribute to the production of colonic-derived uremic toxins such as indoxyl sulfate (IS) and p-cresol sulfate (pCS), initiating a vicious cycle.[12,14,15] These uremic toxins are produced in the colon via protein fermentation. P-cresol is generated via the partial breakdown of tyrosine and phenylalanine by many intestinal obligate or facultative anaerobes including the genera *Bacteroides, Lactobacillus, Enterobacter, Bifidobacterium*, and *Clostridium*.[12,14,16] Indoles are produced by the metabolism of dietary tryptophan by tryptophanase in intestinal bacteria such as *Escherichia coli* (*E. coli*)*, Proteus vulgaris*, and *Bacteroides* spp.[12,14,17]

The accumulation of IS and pCS in CKD has been associated with progression of the disease by promoting renal fibrosis, by inducing inflammation and damaging renal tubular cells, and by stimulating the progression of glomerular sclerosis.[18-22]These uremic toxins also contribute to morbidity and mortality by impairing the neurologic system,[23] lowering erythropoietin (EPO) production[24] and bone turnover, and increasing the risk of cardiovascular disease.[25-27]

Although there is relatively limited information regarding the microbiome and uremic toxins and their link to kidney disease in veterinary medicine, cats with CKD have been documented to have a fecal dysbiosis characterized by decreased fecal microbial diversity and richness based on 16S ribosomal rRNA gene sequencing.[28] It has also been demonstrated that IS is elevated in cats with CKD and is associated with disease progression.[29,30] Serum pCS concentrations are also elevated in some cats compared to healthy geriatric controls.[28] Interestingly even IRIS Stage 2 cats have been documented to have uremic toxin concentrations that are significantly higher than control cats.

Fecal Fatty Acids in CKD

Additional metabolites of colonic bacteria that could be disrupted by intestinal dysbiosis are fatty acids. The short-chain fatty acids (SCFA) produced by the colonic microbiota consist of the straight-chain SCFAs acetic acid, propionic acid, butyric acid, valeric acid, and the branched-chain (BCFA) SCFAs isovaleric acid and isobutyric acid. Straight-chain SCFAs are major end-products of saccharolytic fermentation of complex polysaccharides (including non-digestible dietary fibers) and epithelial-derived mucus and are essential nutrients vital for both intestinal and host-health.[31] They have several beneficial local and systemic effects including promotion of colonic motility, lipid and glucose metabolism, blood pressure regulation, and anti-inflammatory properties.[32-37] In contrast, BCFAs represent only a small portion of total SCFA production, and are produced when protein passes through the small intestine unabsorbed and protein-derived branched chain amino acids are fermented by microbiota in the colon.[31,38,39] Branched-chain SCFAs and other products of protein fermentation in the colon are considered deleterious to the gut, and may serve as an instigator of inflammation as well as have negative effects on motility.[7,38,39]

In humans, dysbiosis in CKD is associated with a decrease in bacteria that produce short-chain fatty acids, but to the best of our knowledge branch-chain fatty acids have not been studied.[15] A recent veterinary study assessed fecal concentrations of short-chain fatty acids (acetic acid, propionic acid, butyric acid) and branched-chain fatty acids (isobutyric acid, isovaleric acid, valeric acid) in CKD cats and normal controls.[40] CKD cats had increased fecal isovaleric acid, in particular IRIS stage 3&4 CKD cats. Cats with muscle atrophy had higher fecal BCFA concentrations compared to cats without muscle atrophy. These findings support malassimilation of protein in cats with CKD.

The Gut as a Potential Therapeutic Target

Due to the potential negative effects of uremic toxins, and their poor ability to be removed via hemodialysis, human medicine has focused on strategies to decrease production of IS and pCS including modulation of bacterial growth in the colon by dietary management,[41] prebiotics, probiotics, and target adsorption of uremic toxins by the use of adsorbents.[10,12,42] The generation of IS and pCS can be modulated by selectively increasing saccharolytic and reducing proteolytic bacteria in the colon and by increasing intestinal transit time (thus addressing constipation is an important consideration). Prebiotics and probiotics have been shown to influence the composition of the colonic microbiota and have been successfully used to decrease IS and pCS concentrations in human CKD patients.[43,44] In addition, increasing carbohydrate and fiber and decreasing protein intake have been shown to decrease IS and pCS concentrations.[41,45,46] Adsorbents such as sevelamer hydrochloride and AST-120 also are used to limit intestinal absorption of IS and pCS.[47,48] In veterinary medicine, there has been little published on strategies to decrease gut-derived uremic toxins in CKD patients and further exploration as a potential therapeutic target seems warranted.

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NOTES:

Feeding Senior Cats for Life-Managing Common Concurrent Needs

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Aging is not a disease

What is a senior cat?

Lifespans of pets are increasing and thus both the percentage and the age of elder cats seen by veterinary health care teams may be increasing.[1] The point at which a cat progresses from adult to a senior or geriatric life stage is variable and subjective. Cats' life expectancies vary widely but with good healthcare, cats are living into late teens or even twenties. Physiologic changes associated with aging may include loss of senses (hearing or vision), reduced energy requirements and lean body mass as well as a decline in various organ functions[2-4]. The American Association of Feline Practitioners published Senior Care Guidelines and suggest that, most cats reach 'mature' or "middle age" by 7-10 years of age and should be considered "seniors" by 11-14 years of age and 'geriatric' when 15 years of age or older.[5] The word 'senior' is used as a broad category to encompass all older cats. Despite this arbitrary categorization, physiologic changes may develop in middle-aged and senior cats making them less tolerant of nutritional deficiencies or excesses. Middle aged pets are more vulnerable or "at risk" for age-related health problems. Middle age may bring an increasing incidence of chronic diseases, many of which can be influenced by nutritional management.[6] Thus a vital component of preventive medical care should include a "senior" screen or health risk assessment for early detection of health problems and adjustments to their care aimed to prevent or slow onset of age-related diseases. Every senior health screen should include a thorough nutritional assessment followed by an individualized nutritional recommendation.

What is a senior cat food?

Pet owners perceive that most pets, including senior cats are healthy and do not require a therapeutic food, [7] but they are still left with hundreds of pet foods to choose from. Advice and information recommending *the* best food is available almost anywhere; from breeders to pet food retailers, from magazines, internet sources and social media. Most cat owners' believe that senior cats have different nutritional needs than adults with seniors, and seek foods labeled for mature life stages. However it is important to remember that there is **no** established Association of American Feed Control Officials (AAFCO) nutrient profile for a "senior" life stage, thus the nutrient content of products marketed for senior pets varies widely. There can be a wide discrepancy between perceived needs of senior pets and actual diet composition of products marketed for them. In addition, there can be significant variation in the nutrient composition between senior cat diets even produced by the same pet food manufacturer. This makes it even more critical for the veterinary health care team to play an active role in providing credible nutritional advice, especially for senior cats that have unique nutritional concerns.

Performing a basic nutritional assessment

Most pet owners recognize that nutrition is an important element of good health, as well as a key way to nurture and care for their cat. With so many confusing messages through media and lay sources, cat owners are searching for credible nutrition information. Therefore, it is crucial the veterinary healthcare teams provide a nutritional assessment for every cat at every visit. This process can quickly identify nutritional risk factors and determine if a more in-depth evaluation should be done to fully assess and make nutritional recommendations. An assessment of all patient's nutritional status is now considered a fifth vital assessment.8-9 Every nutritional assessment and recommendation should include 3 components: the patient, the diet and feeding management factors9. An accurate diet history is invaluable when assessing of the nutritional health of the patient and will be vital to formulating an individualized diet plan. Understanding the nutritional changes that occur with aging and identifying any changes in the individual patient can help the clinician better match the appropriate food with the feline patient's unique needs. The cat, the food and the pet owner's feeding practices are interrelated and require reassessment. Health and nutritional status are not static especially in senior pets, but rather a dynamic process worthy of continued re-evaluation and treatment modifications to match changing needs of the cat. The Canadian Veterinary Medical Association has created a video demonstrating the nutritional assessment process for healthcare teams: https://www.youtube.com/watch?v=3qIIsZY5hRs&feature=youtu.be.[10]

Assess the cat

An initial assessment of the senior cat can be done quickly and utilizes information collected as part of the health assessment: a complete medical and diet history and a thorough physical examination and appropriate lab work (**Table 1**), CBC, serum biochemical profile, urinalysis and thyroid function, blood pressure). The nutritional screening process (**Table2**) can quickly identify patients with "nutritional' risks. Healthy senior cats, (those without identified risks), who are eating a nutritionally balanced diet, have a healthy body weight, body and muscle conditions (BCS, MCS) and are free of significant physical or laboratory abnormalities need no further evaluation at this time, but a follow up plan of when to next assess. A pet-specific nutrition assessment and recommendation for *healthy* seniors

can be done quickly. Nutritional recommendations should include: the specific name of food that matches the pet's current nutritional needs, the amount and frequency for feeding and a monitoring plan. In many of these patients, the feeding recommendation involves little or potentially no change, but should confirm and validate for the owner that the current food and feeding plan does meet the cat's needs and document the current feeding plan in the medical record.

If nutritional risk factors or age-related problems are identified, an extended evaluation and management plan is indicated. This in-depth evaluation should address some common age-related diseases that may be influenced by nutritional management, such as; obesity, arthritis, chronic kidney disease, hyperthyroidism, lower urinary tract disease, diabetes, adverse food reactions, enteropathies, or dental disease.

Assess the diet
A complete diet history is important for evaluating the pet's current nutritional status. Ideally you would like enough information that you can reproduce the cat's exact diet (brand and amounts eaten). The diet history should identify all snacks, treats and nutritional supplements by type and amount. The drug/supplement history should include questions about the use of food to administer medication, as it may comprise to a significant portion of the cat's intake. Diet history information combined with the patient assessment provides information about the patient's daily caloric requirements and specific nutrient intake. This nutrient intake should be compared to the patient's individual needs. For example, healthy or underweight cat with a modest appetite, should be fed a calorie dense product unless otherwise contraindicated.

Quickly assessing the quality of diets can be challenging to members of the veterinary healthcare team. To assist with this process, the World Small Animal Veterinary Association (WSAVA) has recommended criteria for selecting high qualityfoods:
(https://wsava.org/WSAVA/media/Documents/Committee%20Resources/Global%20Nutrition%20Committee/English/Selecting-the-Best-Food-for-your-Pet.pdf. High quality products should have the following features: a complete and balanced cat food, be produced by manufacturers who hire full time PhD or board certified veterinary nutritionists™, have excellent quality control measures, and be able to provide nutrient information. Some of this information for pet food produced in North America can be found quickly by using a tool (Dare to Ask, We Did) created by the Pet Nutrition Alliance (www.petnutritionalliance.org). This resource was designed to help veterinary healthcare teams find unbiased information to make more informed decisions when recommending pet food for their patients.

Assess the feeding management (environment)
Feeding practices and preferences certainly influence a cat's intake. Does the cat have a quiet and safe place to eat? Is feeding part of the cat's environmental enrichment? (food puzzles or opportunities to 'hunt' their food? Determine whether other pets present competition or limit access to a cat's food. Determine whether food is accurately measured, how much/ how often food is offered and how much is eaten. If a cat has a healthy body condition and eats ad libitum, this does not need to change, except to measure intake if possible, and provide that amount, but offer access ad libitum. By measuring the food offered, it is easier to tell when intake declines and is an important diagnostic tool, or early warning sign. An overweight or obese cat will likely benefit from limited quantities offered in meals. Determine if there have been recent changes to the feeding plan and why, as well how the cat adapted to those changes. This information will allow the veterinary team to determine the nutritional adequacy of the current diet, as well as help identify factors that could contribute potential success or problems with adherence to a new recommendation. Quantifying caloric intake is also an important part of assessing feeding management. This is especially important for overweight or underweight patients so the healthcare team can assess the rest of nutrients provided by the daily calories.

Extended nutritional assessment
All cats should be evaluated with a basic nutritional assessment described previously at every visit in order to proactively evaluate health and well-being. If one or more nutritional risk factors (table 1) are identified an extended nutritional examination is indicated.
Below are examples of common findings of senior cats that may trigger a more in-depth nutritional assessment:

History findings
- The cat is eating a raw or homemade diet. Several cations have described both health and nutritional risks from feeding unconventional diets. If the cat owner is insistent on these feeding practices, veterinarians should consult with a board-certified veterinary nutritionist™ (www.acvn.org).
- Change in body weight
- Using dietary supplements
- Gastrointestinal signs (hyporexia, vomiting, diarrhea)

Physical examination findings

- Unhealthy body condition (BCS ≠ 5/9)
- https://wsava.org/WSAVA/media/Documents/Committee%20Resources/Global%20Nutrition%20Committee/English/Body-Condition-Score-cat.pdf
- Muscle loss as indication by muscle condition score
- https://wsava.org/WSAVA/media/Documents/Committee%20Resources/Global%20Nutrition%20Committee/English/Muscle-Condition-Score-Chart-for-Cats.pdf
- Oral health problems (dental or gingival disease)
- Skin or hair coat abnormalities
- Decreased kidney size on palpation

Reassessment and modification of treatment plan

Nutritional assessment of geriatric pets is an ongoing process. Cats experience a variable and wide variety of metabolic changes as they age. It is important to communicate and engage pet owners to create the expectation of continued reassessment and treatment modifications that accommodate the specific changes observed in each individual cat rather than adopting a "geriatric' protocol. A vigilant monitoring plan allows early detection of problems if they arise and a better opportunity to intervene or modify the pet's individualized nutritional plan (Table 3) to improve the cat's health. Partner with clients to help ensure success and maintain adherence to the feeding and monitoring goals.

Effects of aging on nutrient needs

Water

Elder humans exhibit decreased thirst and drinking when challenged by fluid deprivation. Although unknown in cats, a similar response is expected[6]. Thus water intake should ideally be monitored for changes. Senior cats may also be at risk of dehydration if they have subclinical renal insufficiency. When a senior pet has a good appetite but water intake is suspect, consider ways to increase water intake, such as canned or moist food, multiple ways to offer fresh or flavored water. There is recent evidence that increased feeding frequency and water intake increase physical activity, which can have additional impact to help preserve lean muscle[12].

Energy

There remains a need for more research to better understand the relationship between food intake and energy balance in elder cats[2]. Maintaining a healthy body weight and condition throughout life is well accepted to minimize risks associated with morbidity and mortality[4],[13]. Yet, for cats in the US, being overweight and obese is the most common form of malnutrition, reaching up to 60% of the cat population[14]. Overweightedness and obesity in cats is likely to increase or plateau through adult years, and then decrease in cats over 11 years of age. Whether this weight decrease in senior and geriatric cats is due to the reported decline in gastrointestinal function, reduced food intake, change in energy requirements, onset of chronic disease, or any combination of these is not well known. If cats proactively have proper nutrition, health care and environmental management they should not experience unhealthy weight changes as they approach their senior years. This should be the nutritional and medical goal for pets as unhealthy weight gain exacerbates many age-related conditions. A higher protein to calorie ratio diet would be beneficial to promote ideal weight maintenance in mature cats identified at risk for obesity unless contraindicated by other comorbidities.[15]

Protein

Protein requirements increase with age due to increased protein turnover and reduced protein synthesis[16]. Healthy senior cats do not benefit from protein restriction and may be harmed by limiting dietary protein. Protein restriction of seniors could be more detrimental than protein deficiency in younger animals[17]. As a general guideline for estimating daily protein needs; provide cats; ~ 2 gm protein/lb.$_{BW}$ (5 gm/kg.$_{BW}$) minimum[18-21] . This level of protein intake should minimize risk of protein deficiency. Senior cats may need more than this[21]. Based on the diet history, assure the patient is meeting daily protein needs to minimize loss of lean muscle. Carefully assess MCS to monitor lean muscle mass.

The Conundrum of Comorbidities

Making a nutritional recommendation seems straightforward when the senior pet is healthy or has only a single problem. Challenges arise when patients present with multiple seemingly competing or conflicting comorbidities such as overweight patients with renal disease or cancer and pancreatitis. Except for obesity and osteoarthritis, there is little research in how to manage multiple problems. A general approach is to perform a thorough nutrition assessment and first try and meet minimum nutrient requirements. If a patient is not eating enough to maintain weight, nutritional support is indicated. If the patient is eating, prioritize problems by determining which condition is progressive, or impairing quality of life or imparting the poorest prognosis. Table 3 lists typical ranges of nutrient

Summary
Senior cats are increasingly becoming a sizable proportion of patients seen in primary care. Therefore, a proactive approach to making nutrition recommendations to support optimal health and body condition will contribute to their health span. More frequent health screens beginning when cats become middle aged improve disease surveillance and early detection and medical and nutritional intervention.

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Table 1. Diagnostic Testing and Evaluation for Senior Cats.

Laboratory tests	**Proactive senior cat health screen**
Complete Blood Count (CBC)	Annually after age 7 Semi-annually after age 12
Serum Chemistry Panel	Annually after age 7 Semi-annually after age 12
Urine Specific Gravity (USG)	Annually after age 7 Semi-annually after age 12
Urine Protein: Creatinine** ratio (UPC)	Run if urinalysis shows increased protein
SDMA	In cats with low MCS
Thyroid***	Annually after age 12
Physical evaluations	
Comprehensive physical examination and nutritional assessment	Annually after age 7 Semi-annually after age 12
Weight	At every visit
Body Condition Score (BCS)	At every visit
Muscle Condition Score (MCS)	At every visit
Blood pressure (BP)	Annually after age 7 Semi-annually after age 12

Table 2. Intial Screen: Assessing for Nutritional Risk Factors

Nutritional Screen for Risk Factors	**Require extended evaluation if (✓)**
HISTORY OF:	
Treats/snacks/human foods > 10% intake	
Inadequate information/inappropriate feeding/food	
Consuming unconventional diets	
Previous/ongoing medical problems	
Gastrointestinal signs	
PHYSICAL EXAMINATION:	
Any abnormal BCS (≠5/9 or 3/5)	
Any MCS <3	
Unintentional weight loss OR gain	
New medical condition	
Poor skin hair coat	
Dental disease	

Adapted from Table 2 , AAHA Nutrition Assessment Guidelines. The more risk factors identified, the greater the need for an in-depth nutritonal evaluation and recommendation.

Table 3. Common Nutrients of Concern: Modification Ranges for Managing Comorbidities

Nutrient of Concern	**High nutrient/100 kcal**	**Low nutrient/100 kcal**	**AAFCO minimum requirement* nutrient/100 kcal**
Protein	> 10 gm	< 7 gm	6.5 gm
Fat	> 5 gm	< 3 gm	2.3 gm
Carbohydrate	> 10 gm	< 4 gm	----
Sodium	>250 mg	< 100 mg $_{low}$ < 70 mg $_{ultra-low}$	50 mg
Phosphorus		< 150 mg $_{low}$ < 125 mg $_{ultra-low}$	125 mg
Fiber (total dietary Fiber) TDF	> 3 gm	< 1.75 gm	----
Fiber Crude	> 2 gm	< 0.5 gm	----
EPA & DHA	> 16 mg	NA	NA

*AAFCO 2017

Typical nutrient ranges and AAFCO minimum levels for adult feline maintenance to use as reference when selecting products with nutrient modifications to either enrich or restrict a particular nutrient.

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Feeding Outside the Box: Nutritional Triage to Manage Comorbidities

Julie Churchill, DVM, PhD, DACVN

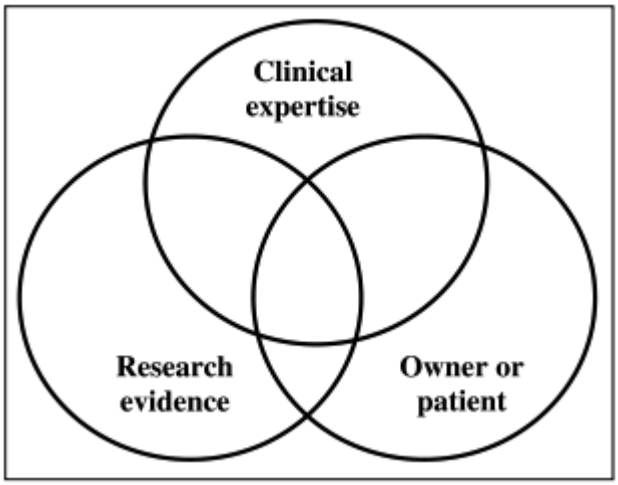
Introduction

Veterinary patients may not present with just one problem. Cats presenting to their veterinary healthcare teams with comorbidities is increasingly common. Therefore, making a nutritional recommendation for them is even more challenging when disease processes require conflicting nutritional management strategies. Research and clinical trial-based evidence may also be lacking about the best practice for nutritional management of patients with multiple conditions or comorbidities. In the absence of such evidence, one approach for these patients is to perform a nutritional triage of sorts, to meet a cat's unique nutritional and life stage needs while also considering nutrients of concern for each condition as well as any contraindications to find a balance or compromised nutrient profile and select the best therapeutic foods to help the whole cat.

Therapeutic Nutrition: evidenced based approach

Evidence based medicine (EBM)

The concept of EBM represents a major but largely untested advance when making clinical decisions to determine patient care. The conceptual model for this suggests that the best clinical decisions are made when high quality evidence from controlled studies, clinical expertise and patient/client preferences overlap:



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High quality research refers to clinically relevant research from patient centered clinical trials. Clinical expertise refers to the use of clinical skills to identify each patient's unique health condition, reach a diagnosis and consider the risks and benefits of potential intervention. A quality of evidence grading scale has been developed:

Quality of Evidence	
Grade	Description
I	Evidence from one or more properly designed randomized controlled clinical studies performed in clinical patients of the target species
II	Evidence from properly designed randomized controlled studies performed using animals of the target species with spontaneous disease in a lab setting or research colony of animals
III	Evidence from appropriately controlled study without randomization, appropriate cohort or case control design using acceptable models of disease or simulations in target species; dramatic result from uncontrolled study or case series
IV	Evidence from studies conducted in other species, report of expert committee, descriptive study, case report, or pathophysiologic justification or opinion of expert based on clinical experience

Although in much of veterinary medicine, there is a paucity of grade I evidence overall. The focus of nutritional research is to evaluate effectiveness of treatment including veterinary therapeutic diets. In the absence of evidence, patients must eat.

Use the circle of nutrition to make a nutrition recommendation, a cat-specific process

Cat's with comorbidities will require and extended nutritional assessment. This process is described in depth previously (Feeding Senior Cats for Life) and should include assessment of 3 components 1) animal factors, 2) diet factors and 3) feeding management or environmental factors. In addition to assessing the patient (species, life stage and comorbidities) the diet must be assessed to assure that it first and foremost meets the unique nutritional needs or the cat and is appropriate for managing disease condition(s). The owner and environment must be taken into consideration as well because it a cat won't eat the food or an owner is not inclined to purchase or feed the food, it is unlikely to be effective. Multi-cat households can also impact the success of a therapeutic diet trial and must be taken into consideration. To complete the process, monitor the cat's response and follow up to make sure it achieves the expected results. If not, reassess and begin the process again. There are many options for therapeutic diets, and it can be difficult deciding which, if any product to use.

Compare nutrients of concern when selecting therapeutic veterinary diets-using information from food product guides

Veterinary Therapeutic diet
Therapeutic (also referred to as prescription diets) are foods used to treat disease or manage/prevent recurrent disease conditions. These products are available through a prescription by a veterinarian and are intended to be fed under their supervision because the nutrient modifications may or may not be intended for long term feeding, and can vary significantly from typical maintenance pet foods.

Look for information containing nutrient parameters of the therapeutic veterinary foods. Commercially available foods also may be appropriate for some of the conditions listed. Veterinarians commonly make a diagnosis, decide on necessary nutrient modifications, and then choose the most appropriate diet for their particular patient. Some foods are used for more conditions than the name implies and "out of the box" or off label use can be a very suitable choice for consideration in patients with comorbidities.

Nutritional therapy for several diseases consists of restriction of nutrient intake, and because many patients with nutrient-sensitive diseases are older and may not eat much, the risk of nutrient deficiencies must be considered. This is particularly true when the therapy is anticipated to continue for months or years. For these reasons, estimates of daily minimum intakes of some essential nutrients may be necessary. The nutrient content of the food must be taken into consideration in the context of total daily intake to assure the cat is meeting its nutritional needs.

Different ways to compare diets:

a. *Diets of similar moisture content and energy density.* One method for comparison is to use the amount of nutrient per unit 'as fed'. AAFCO (Association of American Feed Control Officials), regulations require that minimum percentages of protein and fat, and maximums for moisture and fiber, are reported on all pet foods.
b. *Diets of differing moisture content (e.g., dry vs. canned) and similar energy density*. Another method for comparing foods includes using the amount of nutrient per unit dry matter (DM). Calculate dry matter basis by using "as fed' amount divided by DM of the product. The For example, a dry diet containing 20% protein and 9% water (=91% DM) on an as fed basis contains 20/91 * 100 = 22% protein on a dry matter basis, whereas a canned diet containing 5% protein and 77% water (=23% dry matter) on an as fed basis contains 5/23 * 100 = 22% protein on a dry matter basis.
c. *Diets of differing energy density (e.g., high vs. low fat).* Ideally, the best way to compare all foods, and especially when selecting one for nutritional management of disease, is by the amount of nutrient per 100 kcal - For example, a diet containing 25% protein and 7% fat on a dry matter basis contains 8 grams of protein per 100 kcal, whereas a diet containing 25% protein and 21% fat on a dry matter basis contains only 5 grams of protein per 100 kcal. The therapeutic (prescription) diets report information this way.

To compare nutrient content of a diet with the nutrient needs of a patient, use the amount per unit body weight per day - because many veterinary foods contain restricted amounts of some nutrients, one must compare the number of grams of nutrient in the amount of food consumed with the needs of the cat to ensure that deficiencies are avoided. This is of practical concern for protein and sodium. For example, the minimum protein intake to sustain protein reserves in cats is approximately ~ 2 gm protein/lb.$_{BW}$ (5 gm/kg.$_{BW}$) minimum[1-4]. If a 9 lb. (4 kg) cat with advanced renal failure consumes 300 kcal per day, the diet would ideally contain at least 6 grams per 100 kcal to provide enough protein to meet the cat's needs. If the cat consumed 200 kcal per day, 9 grams protein per 100 kcal diet would be necessary.

Veterinary foods often are formulated to contain "high" or "low" levels of some nutrients. Currently, no generally accepted definition of these terms exists. Based on the nutrient range of therapeutic nutrient profiles and comparison to AAFCO minimum requirements, the author suggests the nutrient modifications listed below as a guideline for consideration when managing feline patients.

Definition of "high" and "low" nutrient densities

Nutrient of Concern	High nutrient/100 kcal	Low nutrient/100 kcal	AAFCO minimum requirement* nutrient/100 kcal
Protein	> 10 gm	< 7 gm	6.5 gm
Fat	> 5 gm	< 3 gm	2.3 gm
Carbohydrate	> 10 gm	< 4 gm	----
Sodium	>250 mg	< 100 mg $_{low}$ < 70 mg $_{ultra-low}$	50 mg
Phosphorus		< 150 mg $_{low}$ < 125 mg $_{ultra-low}$	125 mg
Fiber (total dietary Fiber) TDF	> 3 gm	< 1.75 gm	----
Fiber Crude	> 2 gm	< 0.5 gm	----
EPA & DHA	> 16 mg	NA	NA

*AAFCO 2017

Typical nutrient ranges and AAFCO minimum levels for adult feline maintenance to use as reference when selecting products with nutrient modifications to either enrich or restrict a particular nutrient.

Nutritional triage process

There is little evidence for best practices for managing patients with multiple conditions or comorbidities, yet patients must eat to support their needs and support a quality of life. That authors approach is to perform a nutritional triage of sorts, considering the following elements of the patient's status.

1. Consider medical condition(s) onset- Is it acute or chronic?
2. Prioritize condition(s) impacting clinical signs and the patient's quality of life, and the degree or severity.
3. Prioritize next based on the prognosis and /or progressive nature of each.
4. Consider nutrients of concern or nutritional evidence to:
    - Meet minimum needs for species and life stage
    - Build a nutrient profile wish list(s)
        - Nutrient profile for management of each disease
        - Consider contraindications or intolerance
    - Find a balance or prioritize management of disease(s)
    - Check therapeutic product guides (Nutritional formulary) to think outside the box.
5. Make a Nutritional recommendation
    - Exact product name, form and flavor
    - Specific amount to feed
    - Frequency to feed
    - Monitoring or follow up plan

The remaining discussion will use case presentations of feline patients with comorbidities as examples of the nutritional triage process and diet selection in patient management.

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Cardiomyopathy & Thromboembolic Disease

Ronald Li, DVM, MVetMed, PhD, DACVECC & Joshua Stern, DVM, PhD, DACVIM (Cardiology)

Introduction and Pathophysiology

Feline arterial thromboembolism (FATE) is a known outcome of feline cardiac disease that is estimated to affect approximately 15-40% of cats with cardiac disease. FATE is an acute, life limiting complication with a grave prognosis. More than 50% of cats with FATE will die or be euthanized secondary to this condition. FATE typically results in a thrombus being lodged at the aortic bifurcation and occluding blood flow to one or both pelvic limbs.

Virchow's triad is commonly taught as the pathophysiologic explanation for the formation of the blood clot and includes three principal components, blood stasis, a hypercoagulable state and endothelial damage/disruption. Cats fulfill the criteria of Virchow's triad in a number of ways. The blood stasis required for thrombus formation is generally thought to be secondary to a dilated left atrium with reduced blood flow. This is particularly true in the region of the left auricle, where reduced to non-existent blood flow velocity is commonly seen in cats with cardiomyopathy and left atrial enlargement. Measuring the left auricular flow velocity by echocardiogram can generate estimates of this flow or lack thereof. Endothelial damage or disruption may be seen in cats with cardiomyopathy as well. The left atrial enlargement and stretch may result in endothelial exposure and micro-cracks. Abnormal endothelial exposure may also occur in the coronary vasculature, which is frequently noted to be abnormal in cats with hypertrophic cardiomyopathy. Lastly as cats with HCM may have regions of myocardial ischemia, the regional necrosis seen in some HCM cases may result in endothelial exposure. The final component of Virchow's triad is the necessity of a hypercoabulable state. Cats with hypertrophic cardiomyopathy have been documented to meet this requirement through having activated platelets. Cats with outflow tract obstruction have excess shear stress that is shown to activate platelets. Cats with hyperdynamic left ventricular function (a common observation in HCM) have been documented to have hyperreactive platelets. Cats with a genetic propensity for development of HCM have been documented to have hyperreactive platelets when compared to cats without a genetic mutation. All of these findings support the notion that HCM represents a hypercoagulable state in cats.

The condition of FATE occurs when a thrombus (generally formed in the left atrium or auricle) dislodges from its endothelial attachment and enters systemic circulation. The most common (~90%) final disposition of the thrombus is to lodge in the terminal abdominal aorta at the level of the aortic trifurcation. Some thrombi may find their way to other locations such as the front limb, CNS, kidney, GI tract, etc. While the prognosis for any FATE event is grave, FATE events with thrombi to the forelimb or a single rear limb carry a slightly better prognosis. This lecture hour will focus on the identification and treatment of cats with cardiac disease and ATE from both a cardiology and critical care perspective. The lecturers will use case examples to illustrate their recommendations.

Clinical Signs

Clinical signs associated with FATE vary by the location of the thrombus, size of thrombus (partial versus total occlusion, 1 versus 2 limbs, etc.) and efficiency/ability of the cat to recruit collateral circulation. The most common site of terminal aorta is commonly referred to as "saddle thrombus". The clinical signs of saddle thrombus FATE are classically described by the "5 Ps": pain, pulselessness, paralysis/paresis, pallor, and poikilothermia. Cats with FATE are often initially extremely painful with an acute paretic or paralysis event. Their affected limbs generally lack a pulse and are discolored relative to other limbs with normal blood flow. The affected limb or limbs are cool to the touch. Cats with FATE may present vocalizing, down in the rear limbs and tachypneic. It is important to evaluate whether the tachypnea is secondary to congestive heart failure (a common concomitant condition) or secondary to pain alone. Thrombi that lodge in other organs and do not occlude blood flow to the limb are more variable in their presentation. CNS thrombi may present with neurologic signs. Renal thrombi may result in acute kidney injury. Thrombi to the GI tract may result in abdominal pain and vomiting.

Diagnostic evaluation

A biochemical blood profile is highly recommended, as many cats with FATE will have some degree of azotemia that may warrant therapy. Additionally, continued evaluation (on presentation and throughout hospitalization) of electrolytes, particularly potassium is incredibly important. Hyperkalemia is a life limiting complication of FATE that often ensues with reperfusion injury. Markers of muscle injury may also be severely elevated including CK, AST and ALT. Coagulation testing is not indicated in cases of FATE.

Testing to rule in or out CHF is an important part of clinical evaluation. Thoracic radiographs are frequently used for this purpose but should be avoiding in cats that are unstable/in respiratory distress. An NTproBNP SNAP test can be used to evaluate for possible congestive heart failure in cats and would be an excellent choice in the unstable

patient. Fast thoracic ultrasound is also useful to look for pleural effusion, confirm left atrial enlargement and see signs consistent with pulmonary edema (B lines on ultrasound).

Experienced sonographers may use ultrasound to evaluate the extent and presence of thrombi in the aorta, distal limbs or other vessels such as renal arteries. This technique is not generally necessary for diagnosis but may aid in prognostication.

An echocardiogram is ultimately indicated to evaluate the extent of underlying cardiac disease and evaluate for the presence of additional thrombi in the heart.

Treatment
A hallmark of acute therapy involves pain management. In the author's practice the use of fentanyl or methadone is preferred in the initial management. As the pain reduces over the course of hospitalization many cats can be transitioned to buprenorphine for adequate longer-term pain management.

The presence or absence of congestive heart failure must be carefully considered. Cats with evidence of pulmonary edema or pleural effusion should be treated carefully as an acute CHF patient using oxygen, sedation (typically achieved by the pain therapy already in use), pimobendan, and furosemide. The furosemide dose must be carefully considered in patients with renal thrombi.

Thrombolytic therapy is not recommended in the author's practice, as it has never been documented to improve outcome. Additionally many cats are already establishing collateral circulation at the time of presentation and the use of thrombolytic therapy may further increase the risks of reperfusion injury.

Protection against reperfusion injury is paramount. In the setting of climbing potassium values the use of therapies to lower potassium such as insulin/dextrose constant rate infusions or sodium bicarbonate must be considered. Calcium gluconate may be used for acute cardiac protection during a hyperkalemic crisis. Monitoring of ECG in these hospitalized patients, in addition to frequent electrolyte evaluations is part of their critical care management plan.

Anticoagulant therapy is used to prevent further development of thrombi while the fibrinolytic system continues to break down the current thrombus and reestablish blood flow. Unfractionated heparin in the acute management setting is perhaps the most widely used protocol for ATE cats. In the author's practice the use of low molecular weight heparin is preferred during the initial phase of therapy. Cats are also started on oral antiplatelet therapy, clopidogrel. Using combination therapy is the author's preference for home care of ATE patients. Currently the use of oral clopidogrel (18.75mg PO q24hrs) and rivaroxaban (2.5mg PO q12hrs) is recommended in the author's practice.

Prognosis
Prognostic studies in cats with FATE are outdated and do not represent the current treatment practices proposed by the author. However, the previous publications suggest that only ~50% of cats treated for FATE will survive to discharge and a good portion of those that are discharged (~25%) will succumb to a second thrombus in the future. Poor prognostic indicators that include a low rectal temperature (<99F) and having at least 2 limbs affected have been reported. Anecdotally these numbers are too pessimistic with the currently recommended treatment protocol. Some cats with FATE and HCM with CHF respond very well to treatment and have survival times that mimic CHF alone.

References: available upon request

Additional Reading

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Diagnosis of Comorbidities on a Budget: Practical Diagnostic Options Can Help

Elizabeth Colleran, DVM, MS, DABVP (Feline)

Introduction

According to a study of adults in 2017 by the Urban Institute:
Despite recent economic growth, more than 32 percent of nonelderly adults reported experiencing at least one of three types of financial insecurity in the past 12 months.

Coming up with $400 to cover an emergency expense might seem doable for a middle-class family, but one-third of them couldn't cover that last year. Their experience of financial insecurity underscores their financial fragility despite a growing economy.

These middle-income families earn between $40,840 and $81,680 for a family of three, reflecting the level of income that would place them inside the middle class. But their struggles with financial insecurity highlight how a solid income isn't always enough to cover expenses such as rising rents and health care. The Urban Institute's findings are based on a survey of more than 7,500 adults age 18 to 64. [i]

Whether a feline specialist, a general practitioner or a discipline specialist, the desire to the best for the patient is a primary goal. However, the “best” may be different for the same patient within the context of circumstances and family. The stories are often similar in general terms and can range from simply finding the diagnostic or treatment plan unaffordable to more complex stories of family hardship that can be hard to hear. In any event, the commitment of that family to that cat should not be in question. An effort can always be undertaken to reduce costs while, at the same time, making the outcome less certain. Communication with clients regarding a less financially challenging plan must always be accompanied by the caution that a less comprehensive plan may yield less important information or a less desirable outcome.

Financial matters, however, are not always the reason that the best possible care is declined. Clients will minimize the importance of a health condition explaining the experience they had with other companion cats. Searching the Internet for information on an illness can complicate assumptions that clients make. In the case of natural disaster, such as the Camp Fire in Paradise, CA. financial circumstances may be unknown for a significant period of time following the event. Other complications can be simply a matter of timing; another member of the family has a serious health issue that had a high cost associated with it, for example.

Data

In these and other circumstances, the “best” may be doing as much as can be done by carefully outlining the risks and potential benefits of a “less than optimal” management of this case. Little research exists regarding management of significant illnesses. However, there is some data that may be helpful in planning interventions.

In one study of 15 cats with urethral obstruction for which catheterization had been declined, laboratory diagnostics and abdominal radiographs were performed. Cats with severe metabolic derangements were excluded. They were then managed with a combination of pharmacological treatment, decompressive cystocentesis, and a low stress environment. Treatment was successful in 11 of 15 cats. The authors concluded “this low-cost protocol could serve as an alternative to euthanasia when financial constraints prevent more extensive treatment.” [ii]

Screening in this study for hyperkalemia was done based upon clinical parameters rather than blood tests. None of the cats that were considered qualified for inclusion on the basis of physical examination findings had to be excluded later on the basis of serum potassium concentration or venous pH. In this study, medical records of 223 cats with urethral obstruction were reviewed for signalment, previous medical history, indoor/outdoor status, body weight, clinical signs, physical examination findings, renal function tests, blood gas and electrolyte analysis. Most cats were relatively stable without serious metabolic derangements. Only 12% had severe hyperkalemia. Of all the physical parameters measured, rectal temperature and heart rate were the best parameters for predicting hyperkalemia in this population.[iii] The first author concluded in a 2014 VIN post: “So I often do not do full blood work before (with financial limitations) as you're going to fix the azotemia and metabolic acidosis with your treatment.”

In dermatology, histopathology has been considered the gold standard for diagnosis of most skin and subcutaneous masses. This method commonly requires more sedation, longer procedure times, and more laboratory expense. A definitive diagnosis in these cases, as in most, drives an effective treatment plan. However, when there are circumstances that make this treatment plan challenging promising regarding fine needle aspirate cytology (FNAC),

as an alternative is promising. Samples of FNAC and histopathologic samples of 292 palpable cutaneous and subcutaneous masses were compared retrospectively, 50 of them from cats. Overall, the cytological diagnosis was in agreement with the histopathologic diagnosis in 90.9% (221/243) of cases. The authors conclude: "The results of this study confirmed FNAC as a reliable and useful diagnostic procedure for the evaluation of palpable cutaneous and subcutaneous lesions in small animal practice." While this is not perfect, it may indeed be a satisfying choice when necessary for dermatology cases.[iv]

Management

Following the Camp Fire, our practice held 66 feline evacuees in a space were fewer than 20 could be thoughtfully housed. Most of the people affected by the fire were, quite literally, running for their lives. 23,000 homes were destroyed as well as 1500 businesses. 88 people were killed due to the fire. The people who came to us were, by and large, not our clients. Most were homeless in hotels, tents, friends' and relatives' homes or anywhere they could find shelter. They appeared at our practice desperate and in shock. There were 5 veterinary clinics destroyed and the rest closed in Paradise, California, a town about 12 miles from us. Access to clinical history and medical records was impossible. As people left to find shelter for themselves and their other pets there was little time to even gather brief histories or vaccine records. Many people were insured, others under-insured and the rest not at all. No matter which circumstance, no money was immediately available to pay for care. Our goal was to keep the cats safe and to reassure their owners. Anything more was impossible.

Our primary objectives were to limit the stress already high, keep them eating and free of communicable diseases related to the stress of crowding, not to mention the instantaneous movement out of the home range of a territorial creature. These seemingly modest objectives were not. We moved enclosures, borrowed banks of enclosures, took over rooms meant for offices, break room, bathroom and other intended uses. The principals of Cat Friendly Practice (CFP) were the foundation of our plans. No cats were housed in such a way that, were they unknown to one another, could they be seen. Feliway diffusers were plugged in; blankets covered enclosures of particularly anxious cats. The upstairs storeroom was turned in to another cat room and unrelated cats housed separately.

We employed little pharmaceutical therapy though we did feed a diet containing alpha-casozepine. Cats who didn't eat after 24 hours were given either Mirataz, Cerenia or both. Within 36 hours, all 66 cats had eaten. The last cats went back to their owners 3 months later. Because insurance claims take time, there was no money for anything other than a safe space. No work ups were done and no procedures. Each cat was examined initially and assessments made. A doctor regularly looked, often briefly, at each cat. As the cats began to be discharged a recommendation for each one was made to follow up with their regular veterinarian when possible or our practice if not. Despite the crowding, stress and other circumstances, employing CFP discipline meant that all the cats ate within a short time and there was not a single outbreak of upper respiratory illness.

Case 1

Boots a 9 yo Spayed female Ragdoll year old presented for a painful left eye that was quite swollen and had a central ulceration. The family had been evacuated in the Camp Fire and lost everything. She lived for 3 weeks in 2 different shelters and was finally reunited with owner who was living with friends. She was eating poorly, socializing little and hiding. Her eye demonstrated a defect illuminated by fluorescein that occupied 1/3 of the cornea. Due to insurance claim payment delays the owner could not afford the recommended therapy. Adjustments were made until such time as the client could afford them.

Case 2

Kodiak, a 10-year-old neutered male domestic shorthair presented with a history of hyperthyroidism and for losing weight with a ravenous appetite. The owner had young children at home and finances were sorely limited. Minimal baseline blood work showed no explanation for symptoms as hyperthyroidism was well controlled. The owner declined ultrasound and exploratory with biopsies has the clinician suspected Inflammatory Bowel Disease (IBD). After a long discussion about risks and potential outcomes, the cat was started on typical therapy for IBD. Four months later he had gained weight and therapy was discontinued. One month after that, the client could finally afford a urinalysis. This demonstrated IRIS 1 Chronic Progressive Renal Disease. The cat was started on Calcitriol and an affordable method of monitoring response to this therapy was created.

Case 3

Snowball is a 2-year-old spayed female domestic shorthair who went missing during the Camp Fire. The owner lost her home so the cat, when found 2 months later, was living with the adult child of the owner. The cat on presentation was critically ill, hypothermic, vomiting, anorexic, and anuric. Supportive care was initiated. A marked pyuria was found on urinalysis (Culture was declined) and very high renal parameters including hyperkalemia. Intensive care was recommended with hospitalization that could have been as much as a week in duration. The owner declined. Having informed the owner that the prognosis was likely grave without aggressive therapy, broad-spectrum

antibiotics, subcutaneous fluid instructions give, and other medications and supportive care organized to take place at home. One month later the cat's renal parameters had vastly improved but still indicated IRIS 2 CPRD. Urinalysis demonstrated a resolved pyuria. Calcitriol was commenced and the other medications tapered or discontinued. Monitoring for calcitriol response was abbreviated from recommended tests to monitoring serum Calcium and Phosphorus and renal parameters. The cat continues to improve.

Case 4

Lucy is a 13-year-old spayed female Domestic Shorthair seen elsewhere in 2012 and 2018 for inappropriate urination. She presented to our doctors in 2019 for the same symptoms as well as barbering her coat and weight loss. Ultrasound guided cystocentesis was performed and revealed multiple radiopaque stones and a thickened bladder wall. In-house culture was positive for bacterial infection. The owner could not afford both MIC and a reference lab full blood work up so elected to submit urine only. The remainder of the reference lab work up was cancelled and a brief in-house chemistry and CBC were performed. The types of stones and options for resolution were discussed. The owner could not afford surgery at any time in the future should it be necessary. . A dissolution diet, pain management and appropriate antibiotics were commenced. Two months later, the stones were gone; the cat had gained weight and was urinating appropriately.

Case 5

Madeline is a 6-year-old Russian Blue spayed female indoor only cat. She presented for a second opinion with fever, painful dentition, hyporexia and weight loss. She had previously been diagnosed with pancreatitis and hepatocellular disease. Biopsies were recommended and declined though an ultrasound had not yielded any abnormalities. She was given a 6-week course of prednisolone and her liver values returned to normal. The owners noted that she seemed to have a great sensitivity to routine and declined whenever the owners were away. At the time of presentation she was receiving 50 mg Gabapentin 2-3 times a day for anxiety. On ultrasound her pancreas was large and hypoechoic to peripancreatic fat, gall bladder was dilated, as were bile ducts. She had multiple resorptive lesions when examined while sedated. The goals were to get her out of pain from her dentition, and abdomen, intervene before owners' travel to reduce chance of recurrence of pancreatitis and treat the pancreatitis that she presently had. Reducing overall stress was the end goal. After 14 days of typical therapy for pancreatitis she was much improved and medications were tapered or discontinued. Extractions were performed. At 30 days, she was interacting normally with the family, not hiding and blood work confirmed that she was improving. At 4 months, all of her work up was normal and she had gained weight.

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Heart Disease & Respiratory Disease in the Cat

Ronald Li, DVM, MVetMed, PhD, DACVECC & Joshua Stern, DVM, PhD, DACVIM (Cardiology)

Introduction

Discerning congestive heart failure from respiratory disease can be a challenge in small animal patients. Cats are particularly difficult to make this distinction given their frequent presentation in respiratory distress, which may limit the safety of advanced diagnostic testing. For example, the requirement to provide supplemental oxygen may make obtaining thoracic radiographs impossible. The clinical signs, physical examination findings and sometimes even the changes observed on thoracic radiographs can be quite similar and make the determination of cardiac versus respiratory disease difficult. Additionally, some feline patients may have a component of both respiratory and cardiac disease that further complicates their diagnosis and therapy.

Two of the most common diagnoses for cats in respiratory distress are congestive heart failure (typically secondary to hypertrophic cardiomyopathy) and asthma. Additionally, many other respiratory conditions may present in a similar fashion to congestive heart failure such as interstitial lung disease, non-cardiogenic pulmonary edema, pneumonias and pleural effusions of etiologies other than heart disease. This lecture hour will be presented from both a cardiology and critical care perspective and use case examples to highlight the recommendations of the presenters.

Presentation, Signalment & Clinical Signs

Upon presentation cats with asthma versus those with congestive heart failure may be indistinguishable. Both conditions frequently present with acute onset of respiratory distress characterized by tachypnea and increased respiratory effort. Signalment may provide a good starting point for prioritizing heart disease versus pulmonary disease. For example, a Maine Coon or Ragdoll cat that presents as an adult with respiratory distress is more likely to be diagnosed with congestive heart failure than other non-purpose-bred cats due the increased incidence of inherited hypertrophic cardiomyopathy in these breeds.

Clinical signs are an important consideration for patients with respiratory distress. A careful review of the patient's history may reveal similar reports for cats with heart disease or pulmonary disease. General malaise, exercise intolerance or inappetance may be referable to either primary disease process. One segregating historical report is the presence of cough. In cats, coughing is exceedingly rare in cardiac disease and quite common with bronchial disease, such as feline asthma.

Given the relative instability of feline patients in respiratory distress, the remainder of the proceedings will focus on a step-wise approach to the cat in respiratory distress. The aims will focus on stabilization and identification of the etiology of clinical signs into either a primary cardiac or pulmonary category.

Initially many feline patients present unstable with rapid, shallow breathing. In the author's experience, these patients are best managed with only brief assessment of vital signs and placed in supplemental oxygen. If patient stability allows it, cardiac and pulmonary auscultation, assessment of perfusion parameters, and depending on the relative level of perceived distress to the patient, a small dose of sedation or anxiolytic medication is often administered. The author's preference is to use a 0.2mg/kg dose of butorphanol intravenously or intramuscularly. This initial evaluation may be performed with flow-by or mask administered oxygen. Additionally, an intravenous catheter may be placed and a blood sample taken from the catheter during placement. This catheter may allow administration of life-saving drugs and obtaining blood prior to therapeutic intervention may be useful in assessing renal function, cardiac biomarkers, etc. Unfortunately, much of the information gleaned during this brief evaluation is not helpful in differentiating respiratory versus cardiac etiologies. It is important to remember that many feline patients with congestive heart failure will have no appreciable heart murmur and likewise many feline patients without underlying heart disease may have functional or innocent heart murmurs.

Thoracocentesis and Fluid Characterization/Cytology

Patients with rapid shallow breathing should raise the index of suspicion for possible pleural effusion. This is commonly identified in cats with respiratory distress. In the case of moderate to large volume effusions, thoracocentesis may be both diagnostic and therapeutic. Fluid consistent with exudate may contain inflammatory cells and infectious agents (pyothorax), blood may indicate a coagulation problem or trauma (hemothorax), and chylous, transudate or modified transudate effusions may support multiple etiologies (heart failure, etc). Thoracocentesis may be required expediently as the only intervention likely to relieve respiratory distress in many of these patients.

Empiric Therapy
Empirical therapy may represent an important part of the emergent management in feline patients presented for respiratory distress. Although some patients will become more stable with the aforementioned therapy alone, others will require additional intervention. In these unstable patients, the challenge is to weigh the risk and benefits associated with further stress of diagnostic tests versus empiric therapy. In the author's experience many of these patients will receive empiric therapy for both heart failure (1-2mg/kg of intravenous furosemide) and asthmatic crisis (inhaled albuterol). Ultimately the goal for these patients is to obtain a more stable condition that permits full physical examination and additional diagnostic tests. The prioritization of diagnostic tests is imperative. The author prefers to proceed with fast thoracic ultrasound followed by thoracic radiographs when appropriate.

Thoracic Ultrasound
Thoracic ultrasound is a powerful tool in the diagnostic assessment of cats in respiratory distress. Brief evaluation may provide information on the presence or absence of pleural and pericardial effusions. The presence of pericardial and pleural effusions makes heart disease the most likely etiology. Additionally skilled sonographers may have the ability to identify the cardiac structures and determine the presence or absence of cardiomegaly, most importantly left atrial enlargement, which would prioritize congestive heart failure as the most likely etiology. Other more rare conditions are also easily identified with this test, which include diaphragmatic hernias, peritoneopericardial diaphragmatic hernias and mediastinal mass lesions. A protocol for using the identification of B lines as evidence to support congestive heart failure performs quite well for discriminating heart failure from other origins of respiratory distress. Training modules for these fast thoracic evaluations are available for practitioners to improve their technique.

Thoracic Radiographs
Thoracic radiographs are an important step in characterizing the severity of pulmonary or cardiac pathology. Although significant heart disease may remain radiographically silent in terms of heart size due to the concentric nature of hypertrophy in HCM, left atrial enlargement and pulmonary venous enlargement are frequent features of CHF in cats. Much as significant heart disease may appear as a normal cardiac silhouette, acute bronchoconstriction may also be relatively unimpressive on thoracic radiographs. These situations aside, severe interstitial lung disease may be readily identified on thoracic radiographs in many cases. In feline asthma, hyperinflation of the lungs is a characteristic lesion that is frequently observed and seen as flattening of the diaphragm and increased space between the diaphragmatic margin and cardiac silhouette. It is important to remember that despite the size and shape of the cardiac silhouette, echocardiography remains the only test that can definitely confirm or deny the presence and variety of heart disease. While this test is not usually necessary during the acute management phase, eventual evaluation by echocardiogram is generally warranted in feline patients with suspected heart disease.

Electrocardiogram
Electrocardiography may represent an easy diagnostic test that could increase suspicion of primary cardiac disease. Ventricular and atrial arrhythmias are frequent features of cats with underlying heart disease. Additionally, patterns of chamber enlargement may be readily identified and if present are a reliable indication of heart disease (R wave amplitude >0.9mV). Unfortunately the electrocardiogram remains specific but not sensitive for identification of heart disease.

Cardiac Biomarkers
Cardiac biomarkers have an emerging role in the assessment of patients with possible heart disease. The most important of these are cardiac troponin-I (cTNI) and NT-proBNP. Elevations in either cTNI or NT-proBNP have relatively good sensitivity and specificity for the confirmation that respiratory distress is secondary to congestive heart failure. For cTNI, one study identified that elevation beyond normal reference range had a 100% sensitivy but only 58% specificity, while significant elevation was highly specific but relatively insensitive. NT-proBNP performed a bit better with elevations well characterized in multiple studies as highly suggestive of signs referable to primary cardiac disease. The primary problem with relying on these tests is the general availability of results in a reasonable time period. While cTNI may be measured bedside, it is not typically a diagnostic capability of primary care veterinarians. Importantly NT-proBNP is now available as a bedside SNAP test. While the measurement cut-offs do represent a limitation of the test, the utility will be further discussed in the lecture hour. NT-proBNP is also available as a send out test that requires an approximate 24-hour turnaround time. The development of bedside NT-proBNP testing represents a major advantage in assessment of feline patients with respiratory distress and ongoing research is investigating this test use.

Conclusions
Determining the etiology of respiratory distress is a diagnostic challenge. Future release of bedside biomarker tests may improve our emergent diagnostic capabilities. In the meantime, signalment, history, physical examination, brief

thoracic ultrasound, chest radiographs and possibly electrocardiogram are generally sufficient to proceed with a reasonable therapeutic plan. Oftentimes response to therapy provides the most solid conclusion on the origin of the respiratory distress. Furosemide or albuterol trials are reasonable therapeutic and potentially diagnostic interventions in feline patients with respiratory distress. Lastly, the fragility of these patients cannot be over stated and the clinician should exercise extreme caution and minimize stressful diagnostics when possible.

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Hypertrophic Cardiomyopathy & Co-Managing Hypertension or Hyperthyroidism

Joshua Stern, DVM, PhD, DACVIM (Cardiology)

Introduction

Hypertrophic cardiomyopathy is the most common cardiac disease in the cat. It has been documented to affect 1 in 7 cats (14%) compared to it's known prevalence of 1 in 500 human beings. HCM is primarily characterized by non-physiologic hypertrophy of the left ventricle and resultant diastolic dysfunction. The cause of HCM is genetic with multiple mutations identified in purebred cats to date. This lecture will highlight the pathophysiology of HCM, diagnosis of HCM, preclinical therapy for HCM and therapeutic options for symptomatic patients with HCM, and outcomes of disease. This lecture hour will further focus on using clinical cases to discuss the intersection of HCM and systemic hypertension or hyperthyroidism.

Pathophysiology

Hypertrophied myocytes with disorganized sarcomeric alignment are hallmark histopathological changes in HCM. The hypertrophied myocytes may possess unusually shaped nuclei and chaotic myofibril alignment. They also frequently have abnormalities in the coronary arteriolar walls, elongation or malformation of mitral valve leaflets and presence of myocardial fibrosis, leading to further functional abnormalities of the heart.

Primary components of the functional disturbances observed with HCM are reduced stroke volume with diastolic dysfunction, reduced chamber size, and decreased compliance of the left ventricle (LV). Stroke volume can be even further reduced by the presence of left ventricular outflow obstruction (LVOTO). LVOTO most commonly develops secondary to systolic anterior motion (SAM) of the mitral valve or mid-ventricular obstruction generating mechanical interference along the pathway of the LV outflow tract. This causes increased pressure in the LV lumen and elevated flow velocity through the LV outflow tract. Elevated LV outflow tract velocity can further worsen SAM and lead to the development of mitral regurgitation LVOTO can also occur at the mid-cavity or apex of the LV lumen resulting from symmetric or asymmetric hypertrophy of LV anterior and posterior wall. Therefore, the degree of reduced stroke volume due to HCM may vary depending on the degrees of diastolic dysfunction, myocyte hypertrophy, LVOTO, mitral regurgitation and cardiac systolic dysfunction. Additionally, it is important to note that LVOTO may be dynamic and often dependent on physiological state, making its presence more common and more severe with exercise or catecholamine stimulation. The imbalance of muscular hypertrophy with poor coronary blood flow sets the stage for myocardial ischemia as a common component of this condition. This further complicates the clinical picture of HCM adding ventricular arrhythmias and myocardial infarction to the list of disease sequelae that must be considered.

Clinical manifestations of feline HCM vary from asymptomatic to serious complications such as sudden death (SD), congestive heart failure (CHF) and thromboembolic disease. Feline HCM is most commonly associated with congestive heart failure (CHF) with pulmonary edema and pleural effusion. In one clinical study of cats with respiratory distress, more than 50% of those diagnosed with CHF had HCM. This high prevalence of CHF in cats with HCM might be associated with the significant phenotypic and genotypic differences between humans and cats. Another possibility is that feline HCM is more prevalent in apparently healthy patients and we simply don't see these healthy cats in veterinary hospitals due to a lack of standardized screening protocols. Supporting this hypothesis is a study that screened apparently cats by echocardiography and ECG, which found HCM in 14.7% of the population. This data more closely resembles the high number of asymptomatic human HCM cases.

Feline HCM is an inherited disease with known causative mutation in two defined breeds. Where mutations are defined it is inherited in an autosomal dominant pattern with incomplete penetrance. In 2005, the first genetic mutation associated with feline HCM was identified in the MYBPC3 gene of Maine Coon cats. Shortly after, a second mutation in the same gene but at a difference locus was also identified in Ragdoll cats. Among these mutations, A31P missense mutation in MYBPC3 gene is the most common and present in approximately 30-40% of Maine Coon cats. Young male cats are overrepresented to develop HCM, but female Maine Coon cats tend to develop HCM later in their life with milder clinical signs than male Maine Coon cats.

Diagnosis of HCM

The gold standard diagnosis of HCM is made by echocardiogram. The diagnostic criterion for HCM is based upon the finding of a single left ventricular wall segment (not associated with a papillary muscle or moderator band) that exceeds 6mm in diastole. These measures may be made in m-mode or 2D mode. Secondary echocardiographic findings that support the diagnosis of HCM are the presence of obstruction, left atrial enlargement, visualization of auricular thrombi, or evidence of diastolic dysfunction via transmitral filling profiles. There is some evidence that the

6mm cutoff may be too high for small cats.

With HCM having such a high prevalence in the population, the application of screening tests that are affordable and accessible to private practitioners is extremely important. The use of cardiac biomarkers has been well studied in feline HCM. Currently the best performing cardiac biomarker is NTproBNP. When screening for occult HCM, the use of a quantitative NTproBNP test is recommended. While false positive results are possible, an elevated NTproBNP test in a cat warrants echocardiographic evaluation as soon as possible.

Radiographic screening for occult HCM is not recommended as the concentric hypertrophy of HCM can be easily missed in the early stages of disease by radiography.

ECG screening is a reasonable strategy, particularly when auscultation identifies an arrhythmia. The presence of ventricular arrhythmia makes a diagnosis of HCM more likely and would warrant further evaluation by echocardiogram.

For the diagnostic approach to the symptomatic cat, please see the additional notes on respiratory distress in cats.

Treatment of Occult HCM

The evidence supporting preclinical treatment of feline HCM is weak. Empiric therapy is based upon study trends and disease physiology. The use of atenolol as a beta-blocking drug for occult HCM is controversial. It is most widely supported as a mechanism for reducing obstruction in feline patients with HCM and left ventricular outflow tract obstruction (LVOTO). However, even in the absence of LVOTO, the use of atenolol has theoretic benefits. Atenolol may address the potential for ventricular arrhythmias with HCM. Atenolol lengthens diastole and thus increases time for myocardial perfusion, potentially reducing ischemia. Atenolol is cardioprotective as it protects against myocardial fibrosis secondary to excess catecholamines. Atenolol may reduce myocardial oxygen demand by slowing heart rate and lessening response to sympathetic influence. Nevertheless no study has documented a survival benefit for atenolol in occult feline HCM. A single abstract report demonstrated that cats on atenolol had improved quality of life.

Once moderate left atrial enlargement is observed a majority of cardiologists agree that the likelihood of either resultant CHF or thromboembolism is high. Preventative therapy to reduce the likelihood of forming a thrombus is recommended with oral clopidogrel daily. Ace-inhibition with either enalapril or benazepril in an attempt to reduce the drive for cardiac remodeling, sodium and water retention is also sometimes recommended.

Phenocopies of Disease

HCM is a diagnosis that must be made in the absence of disease phenocopies. Phenocopy is a term used to describe a disease that may phenotypically be difficult to distinguish from another condition. In the case of HCM there are multiple disease phenocopies which clinicians should routinely rule out prior to making a diagnosis of HCM. Disease like systemic hypertension, hyperthyroidism, acromegaly, and myocarditis, can look echocardiographically identical to HCM, but require distinct treatment modalities.

Systemic Hypertension as a Confounding Factor

All patients with confirmed or suspected HCM should be screened for systemic hypertension. While systemic hypertension alone could result in an HCM phenotype, the presence of hypertension can also exacerbate already present myocardial disease like HCM. In the author's practice blood pressure measurement via Doppler and sphygmomanometer is performed for all feline patients being evaluated for cardiomyopathy. Technique is incredibly important to minimize white coat artifact. Ideally the measurements should be performed prior to the examination in a quite exam room with the client and after the cat has had some time to adapt to their surroundings. The author's practice records five consecutive measurements and discards the highest and lowest value, while averaging the remaining three measures. If the average value obtained meets or exceed 160mmHg then this patient requires reevaluation and consideration of therapy. If the average value exceeds 180, then workup for hypertension and treatment is considered. In the setting of a patient with echocardiographically identified LV Hypertrophy and documented systemic hypertension, the decision must be made whether the patient requires therapy for HCM or whether it is appropriate to treat the hypertension and reevaluate the cardiac change in subsequent visits. Generally, patients with subclinical HCM and no evidence of left atrial enlargement can be treated for their systemic hypertension and once the blood pressure has returned to normal and is controlled for a period of 6-12 months have a repeat echocardiogram. In the setting of more advanced cardiac disease it may be necessary to treat both the cardiac disease and the hypertension. For example a patient with confirmed left ventricular hypertrophy and moderate to severe atrial enlargement may warrant anti-platelet therapy and ace-inhibition in addition to the use of drugs to lower blood pressure such as amlodipine. The author's practice routinely prescribes amlodipine once or twice daily at a conservative dose of 1-1.5mg/kg to start and up-titrates to effect over the course of weekly

reevaluations until a normal target BP is achieved in the absence of any side effects.

Hyperthyroidism as a Confounding Factor
Similar to systemic hypertension, elevated thyroid level may produce a disease phenotype that mirrors that of HCM or it may exacerbate already present myocardial disease. Any cat that is greater than 6 years old in the authors practice and is diagnosed with left ventricular hypertrophy consistent with HCM should be screened by total T4 level for possible hyperthyroidism. While it seems unusual for hyperthyroidism alone to result in severe disease or congestive heart failure, the concomitant diagnosis of HCM and hyperthyroidism can be quite severe. Similar to hypertension, cats with subclinical cardiomyopathy may be best treated by addressing their hyperthyroidism and reevaluating their echocardiogram after 6-12 months of a controlled thyroid level. Careful attention should be paid to renal values pre and post treatment for hyperthyroidism because the high metabolic rate of hyperthyroidism may mask underlying renal disease which may become readily apparent with treatment and particularly relevant in the setting of residual heart disease.

Treatment of Symptomatic HCM
For the therapeutic approach to the symptomatic cat, please see the additional notes and presentation on managing respiratory distress in cats.

References: Available upon request.

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Layers of Complexity: The Feline Imperative for Integrating Pharma & Non-Pharma

Bonnie Wright, DVM, DACVAA, cVMA, CVPP, CCRP, CCRT

Introduction

Cats are passionately attached to… being cats. While they share >96% genetic homology with other large felids, cats continuously remind us lowly veterinarians that they are truly different from all other species. They get agitated on minor tranquilizers; they vomit on the major ones… They share opioid mediated behaviors with an unlikely group: the horses. All in all, they go out of their way to be challenging to treat; and let's not even begin to discuss how well they hide the *things* that need to be treated.

When it comes to treating pain in any species, it is an emerging realization that a combination of pharmaceutical and non-pharmaceutical tools must be utilized. For example, each of us bipeds who has ever been injured will realize the things like ice, massage and physical therapy are regularly applied to return our function. Cats are just more extreme in this, as in many other, ways. They challenge us with altered drug metabolism, a host of toxicities, an intolerance to being medicated, and the tendency to stop eating anytime we really think they need to eat… Previous lectures have delved into the pharmacologic handling of felines- and now we will dive into non-pharmacologic therapies- which I generally describe as "physical medicine" because these modalities use mechanical or thermal forces to alter tissues, nerves, neurotransmitters, and other biochemical substrates.

Physical medicine modalities

That have been used in cats include acupuncture, stretching, therapeutic exercise, massage, joint mobilization, ultrasound, laser, shock wave therapy, ice, heat and environmental enrichment. Weight loss is an important consideration associated with all species, and although a direct association has not been proved, studies have shown an increased incidence of OA pain in cats with higher body condition scores. (Lascelles BD, 2007) These therapies modify endogenous systems to create change, thereby bypass drug metabolism issues, drug administration issues, and the insecurity that we know what harm a drug can do with so little definitive research in cats. Furthermore, they are often more dramatically effective at reducing behaviors thought to be associated with pain, improving activity, and restoring pet-owner interaction. In treating chronic pain in my everyday life, my approach is nearly always a combination of pharmacology and physical medicine. Finally, there is a very fine line between doing no harm, and the practice of quackery (unfounded belief-system based interventions) when scientific data is lacking. Every person attempting to treat chronic pain in cats is sitting in this undulating line, at least for the time being. We have some pharmacologic data (covered previously), but this is complicated by different opinions, recommendations from the pharmaceutical companies, and the whims of the feline patient that is being offered these treatments. At some point, we simply have to 'practice', and continue to modify as more data becomes available. Humility about our ignorance is paramount to continuing to add knowledge to our practice.

The ubiquitous lack of good data for both diagnosis and treatment of pain in cats follows us into the realm of physical medicine. Much of physical medicine is based on an understanding of physiological mechanisms for healing rather than on objective data. Some of this departure from placebo-controlled trials is the fact that complex interventions are very poorly represented by placebo-controlled studies. (Ted J. Kaptchuk, 2009)[i] Even with a simple intervention (such as swapping a sugar pill for an active drug), the medical ritual surrounding research trials has been shown to alter perceptions in both the 'placebo' group, and the treatment group. This impact is massively heightened when complex interventions such as acupuncture, touch, exercise, diet and lifestyle are implicated in the treatment, as is the case with physical medicine. As such, the physical medicine community is not denying the value of basic science. Conversely, the human physical therapists have recently increased the educational requirements for physical therapists to a doctorate level, in a large part to provide a strong impetus for the accumulation of proven scaffolding for the practices making up physical medicine. Alas, cats will be far behind in the data collection, requiring a physiological explanation for the tools rather than validated clinical trials, for the time being.

Physical medicine at it most simple, is interacting with the analgesic systems provided by an organism and attempting to activate these systems. This occurs along the entire pain sensing system: from skin to brain, and also involves muscle, tendon, fascia, periosteum, etc. Physiology provides a complex, multi-faceted tapestry for both pain sensing and modification of the transmitted signal. The overlap between the nervous system and other endogenous, autonomic systems (such as immune state, GI motility, etc.) that has long been recognized in osteopathic medicine is now becoming main-stream and evidence base is ballooning. Understanding the physiology of nervous system wiring is the first step toward understanding methods to intervene in these endogenous systems and help modify them towards homeostasis. The relationship of many of these modalities with vagal nerve stimulation and interactions opens up a growing field of evidence to help describe the mechanisms for these interventions.

(Browning K, 2017) While pain is a major target, several other conditions applicable to veterinary practitioners are also gaining an evidential basis:

Analgesia (PENG GAO, 2015)
Neurologic injury mitigation and return to function (Qaseem A, 2017)
Gastro-intestinal motility disorders (Li H, 2015)
Orthopedic trauma and return to function (Sullivan D, 2016)
Immune and other homeostatic systems (seizures, immune-mediated conditions) (Kim SK, 2010)

To elaborate on treatments for each of these categories in subsequent lectures today, an understanding of the physiologic underpinnings of physical medicine is required. Physical medicine techniques exploit endogenous physiology in numerous ways:
Temperature related modalities
Tissue deformation
Neuromodulation (peripheral, spinal, and central nervous system)
Muscle spasm, myofascial trigger points, tendon and ligament function
Cartilage health and joint mobility
Modulation of metabolism and blood flow and immune modulation

Temperature-related modalities
Ice (physical) or menthol/peppermint (chemical)-
TRP M8 channels on afferent nerve endings (McCoy DD1, 2011 Jun;300(6))
Activation provides a continuum of cold-analgesia through cold-pain (noxious), as well as voltage-mediated modifications (electrical stimulation and TENS). (Knowlton WM, 2011 Jan 1;12(1))
In addition to modification of blood-flow, inflammation and swelling (Millis, Jan;45(1)) cryotherapy has a discrete biochemical effect on the modification of pain. Most veterinary studies just focus on degree of cooling relative to time (20 minutes appears ideal in most tissues). To understand this biochemistry, we will review the afferent nociceptor, which responds to chemical, mechanical and thermal sources of pain. Transient receptor protein channels (TRP) are ion channels that are distributed on afferent nerve endings and conduct specific sensations. Ice is generally considered for acute injuries (post-op up to day 3), but due to analgesic effects, may be used chronically as well.

Heat: Physical heat (warm packs, hydrocollator packs, etc.) or capsaicin (chemical)
Heat is used to increase blood flow, increase collagen distensibility, and possibly provide mild analgesia (Millis, Jan;45(1)). Ideal temperature has not been elucidated, but a period of 10 minutes is recommended for application (1.5 cm max. depth to surface heating, regardless of application time- for deeper heating see therapeutic ultrasound). In general, heat is used more frequently for chronic conditions, with fibrous, or musculotendinous restrictions, or to help drain edema after it has formed (after approximately the third day after an injury).

TRP V1 channels on afferent nerve endings sense heat. This can be pro-inflammatory or anti-inflammatory (via IL-6 in muscle tissue). (Obi S, 2017 Mar 1;122(3)). In general, heat is not considered directly analgesic at the level of nerve-endings (but see discussion on tissue distensibility, which is likely to provide analgesia to soft tissue restriction secondary to fibrosis and fibrous tissue healing, as well as muscle spasm/trigger points)

Therapeutic ultrasound
Enhances tissue distensibility and wound healing. Heats deeper tissues rather than surface (up to 3 cm). Hair should be clipped (data shows poor heating through hair, regardless of gel). Consider use for deeper heating of muscle and tendon groups. (Millis, Jan;45(1)) Regardless of depth, heating wanes after 10 minutes post-U/S (so need to move to stretching and soft tissue work within 10 minutes).

Tissue deformation
Is a powerful modulator of intrinsic healing in soft tissues such as skin, muscle, ligaments, tendons, fascia, cartilage and periosteum. When tissue is deformed, growth factors and a variety of proteins and neurotransmitters are released, leading to changes in pain processing, metabolic processes, inflammation, blood flow and healing capacity. (HM, 2014) Various techniques, such as: provider-applied techniques (acupuncture, massage, myofascial trigger point release), individual motion (stretching, exercise, physical therapy) and mechanical devices (extra-corporeal shock-wave therapy ECSWT), depend heavily on these physiological networks.

Neuromodulation
Changes neurotransmitters at the skin, along axons, in the spinal cord, interneurons, brain and even in the supportive structures of the glia. These changes can be short term (immediately improving comfort and function) but

can also be long-standing (using plasticity of the nervous system to make structural and permanent changes in pain processing and nerve function). Neuromodulation is intrinsic to the analgesic actions of physical medicine techniques. (PENG GAO, 2015) A vast amount of data is available for this topic, especially in research species such as rabbits, rodents, and sometimes, cats and dogs. While this is HUGELY important in the ICU, I will give it only a small focus in this lecture (or it would take ALL the time), to focus on the less obvious benefits of neuromodulation on ICU patients. The healing effects of physical medicine modalities on the nervous system should not surprise us (as we know that the nervous system functions in a use-dependent pattern), and yet it receives absurdly little airtime.

Peripheral
Triad of peripheral components: cellular, vascular and neuronal crosstalk to amplify or de-amplify peripheral signals, and increase or decrease the receptive fields by modifying the population of peripheral nerve endings.

Spinal
Primary afferent fibers transmit impulses from the periphery through Aδ and C fibers to the dorsal horn of the spinal cord (lamina 1-3 & 5 primarily).

Touch fibers terminate more ventrally in the dorsal horn, in lamina 3-5. Note the overlap in lamina 5. This region is replete with wide dynamic range neurons (WDR) than can transmit a variety of signals. If an impulse such as touch, needle penetration or proprioceptive input (from shaking a burned finger, for instance) bombards the dorsal horn in this region, it causes a transient overload, contributing to a decrease in transmission and amplification of pain signals leaving the region.

Additionally, punctate stimulation of afferent fibers accentuates spinal cord mechanisms of analgesia using enkephalins, endorphins, serotonin, norepinephrine, purines, glutamate, neurokinin, cannabinoid, ion channel modifiers, modification of transcription, and through additional modification of associated cell types such as interneurons, microglia and astrocytes.

Central
Ascending from the spinal cord, the information from aδ fibers are carried to the brainstem for rapid dissemination including alerting and autonomic changes.

C fiber information are delivered to the limbic system, evoking the emotive qualities of pain and misery. Descending modulation includes use of endogenous chemicals such as enkephalins, endorphins, serotonin, norepinephrine, and endocannabinoids. Empiric data on the autonomic and emotive aspect of acupuncture therapy have supported the physiologic assumption that this association with the limbic system could be exploited to a patient's advantage.

Viscero-Somatic inter-relationships
The spinal cord carries all types of nerve fibers, including autonomic, proprioceptive and motor nerve groups. Due to inevitable overlap of input and output from regional spinal segments, there is a great deal of spill-over onto the neurologic framework by both pain and acupuncture. This causes the phenomenon of viscero-somatic and somato-visceral projections, where pain from an internal organ can be referred to the periphery, and vice versa. Likewise, treatment of a regional spinal segment is likely to have effects on related structures that are served by the same spinal segment, but not available for treatment due to their location deep within the structure. This relationship opens up a huge variety of conditions that can benefit from neuromodulatory input, such as electrical stimulation and acupuncture.

Musculo-tendinous function
Much of this section relates to using these systems with deliberate physiotherapy, keeping form and function in mind to avoid as much tissue loss, and encourage earlier return to strength and function.

Muscles show decrease in mass (atrophy) after only two weeks of reduced use, and a single week of immobilization. Type 1 fibers (slow-twitch- static support and proprioceptive) are the most vulnerable. In general, recovery of muscle mass and function takes longer than period of disuse.

Tendons and ligaments: size, fibril structure and organization, collagen biodynamics, HA, chondroitin and water content are all negatively affected by disuse. The tendon-bone interface is the most vulnerable, and the longest to recover (6 weeks of immobilization requires >18 weeks of remobilization).

Myofascial trigger points and myofascial strain patterns
Muscle and fascia live alongside the neurologic framework and become implicated in changes that occur with injury, illness and disease. This can occur in patterns associated with common compensatory muscle groups, or simply in a

spinal-segmental association with the irritable regions of the nervous system. This can be used to aid in diagnosis, monitor treatment success, and contribute to treatment success

With excessive neuronal activity associated muscles spasm and enter into an 'energy crisis'. An initial sustained release of calcium due to muscle splinting and activation results in sustained sarcomere contracture. Increased metabolic rate of these muscle groups is compounded by local ischemia due to the contracted state of the muscle inhibiting local blood flow. Energy in the form of ATP is required to move intracellular calcium back into the sarcoplasmic reticulum at the end of the contraction, which is no longer possible in the sarcomeres anoxic state, thus the high intracellular calcium remains, sustaining the contraction. In addition to be painful of their own right, chronic muscle contraction (trigger points) contribute to changes in movement and put additional strain on joints and/or spinal segments served by the contracted muscle bellies. Over time this 'myofascial restriction' help to create co-morbid conditions that accumulate into a multi-faceted pain experience.

Therapies for myofascial trigger points and strain patterns include acupuncture, laser, heat, stretching, active and passive range of motion, muscle-spindle release mechanisms, mobilizations, massage, and injection or topical application of local anesthetics

Cartilage and Joints
Disuse also causes reduction in bone strength and cartilage health and function. Perfusion of non-vascular tissues, such as articular cartilage and intervertebral disks, is thought to be a dynamic process- with fluids being moved through motor activity and compression/traction cycles (such as walking). Knee loading protects cartilage by decreasing presence of osteoclasts in a rodent study. (Li X, 2016)

Metabolism, blood flow and immune modulation
Vagal nerve input is a powerful modifier of the immune system and may influence CNS excitability (seizure mitigation). (Browning K, 2017) Acupuncture, electrotherapy and exercise are all modifiers of vagal nerve activity. Blood flow is also altered by various forms of physical medicine, and provides dynamic changes in local immune control, deep organ perfusion relative to peripheral stimulation, and delivery of chemical signals for both pain neuromodulation and tissue healing.

Exercise
Physical exercise is analgesic, in addition to providing soft tissue stretching and lubrication. (Naugle K, 2012). Exercise is associated with more rapid recovery after trauma, including brain and spinal cord injuries.

Conclusion
As the literature about pain in cats' trickles into the databases, we will have more and more tools identify and treat their pain. Meanwhile, both the diagnosis of feline pain, and many very effective treatments lie, quite literally, in the hands of the practitioner. An inquisitive, gentle touch often helps locate the specific source of discomfort, perhaps with greater clarity than the classic reliance on radiographic evidence of arthritis (that is frequently poorly correlated with comfort). While the body seems to have any number of ways of amplifying pain into multiple tissue types and even regions, it also holds the keys to homeostasis. We can often gently coax the body back into a place of balance with a combination of physical medicine modalities, pharmacological manipulations, and investment by the owner in exercise, diet, environmental enrichment, and weight considerations.

In the classic story of Winnie, the Poo, the little piglet notes that it is hard to be brave when one is very small. In cats, it is difficult to be brave because our data bank is so very, very small. However, there are many options, and a combination of these options often brings about a very positive outcome. We must guard against causing harm, and also against losing ourselves to unproven treatments, but at the end of the day, we must also treat the feline patients that present for chronic pain. And they are most definitely out there.

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Managing the Peri-Operative Cat with Renal Disease from Start to Finish

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Anesthesia can be done safely in renal compromised patients and should not be blamed as a reason for not treating systemic diseases that result in greater renal compromise (like dental disease).

Managing cats with renal disease that require anesthesia or sedation for procedures is a complex challenge under the best of conditions. Adding to this challenge is that several of the "rules of play" have changed over the previous decade. Of great importance, is: while anesthesia does pose a risk to the function of kidneys, with appropriate management it is possible to anesthetize patients with renal disease without increasing their burden of glomerular loss. Anesthesia can be done safely in renal compromised patients and should not be blamed as a reason for not treating systemic diseases that result in greater renal compromise (like dental disease).

Please consider the notes from the previous lecture on Feline Anesthesia with Concurrent conditions
Much of what was discussed in that hour is the baseline theory for this lecture. In summary, the handling of the WHOLE patient to maximize comfort and minimize stress. In the interest of brevity, this lecture will primarily focus on those things that have changed surround the anesthetic management of RENAL disease, what is the evidence for those changes, and how they fit into the overall management of cats with renal disease.

Continuum of Kidney Disease
It is neither new nor surprising that elective procedures are best scheduled with the most stable possible condition of the feline patient. The International Society of Feline Medicine (ISFM) has published extensive guidelines on the management of feline kidney disease, and these is the current prototype for establishing this stability. (Sparkes et al., 2016) The peri-operative management of these patients, however, doesn't change when compared to the management of emergency cases with kidney disease, where improving IRIS stage or other components of kidney management cannot be addressed.

Volume Status and Fluid Therapy
Massive IV fluids used to be the mainstay of treating renal disease patients during anesthesia. It was common to bring patients in hours to a day prior to a procedure to fluid load, use high intra-operative fluid rates, and continue this into the post-operative period. It has now become clear that rampant fluid loading contributes to acute renal damage through the creation of edema and decreases in filtration capacity at the level of the glomerulus. (Myberg 2013)
It remains true that adequate hydration is critical for the maintenance of renal perfusion and autoregulation, and hydration status can be a illusive measure. A thorough history of fluid intake and fluid loss should be closely considered. In general, a patient with stable kidney disease, being managed with adequate oral fluids and without losses likely does not need fluid pre-loading, although an hour or two and a conservative maintenance rate would not be wrong. The emergency patient is the greater challenge, as either intake or losses may be more difficult to predict, and pre-operative fluid therapy may play a more critical role. Veterinary practice has advanced to where ultrasound is readily available and can be assessed for dynamic rather than simply static changes. Thus, where available and when the hydration status is unclear, rapid assessment of atrial filling and large-vessel filling (aorta, vena cava and renal vasculature) is a sensible approach to determining the need for pre-induction fluid therapy. (Lichtenstein 2014) Where this is not available, a clinician's best assessment of mucous membranes, skin turgor, pulse quality and history are required.

Intra-operative fluid rates are no longer turned up to fluid-loading levels. In general, the recommendation of 5ml/kg/hour that pertains to most anesthetized cats is used, and this is tapered in procedures that last more than a couple of hours to nothing more than maintenance rates. A limited number of fluid bolus' as needed for hypotension may be applied, but as a general rule, no more than about 10-15 mL/kg should be used in this capacity, and if they are used the taper to maintenance fluid rates should be done more quickly, to avoid overall fluid loading during the procedure. The adage that urine production reflects adequate renal perfusion remains truthful, so in more critical cases (either due to their degree of kidney disease, or due to emergency or uncontrolled status), ongoing measurement of urine output is an excellent monitoring tool. This can be done with simple collection methods, or spot-checking ultrasound measurements of either urine flow or bladder size.

Within the category of fluid management, the issue of colloids requires a deep and unapologetic critique. While even recently reported to improve fluid loading and promising longer-duration improvements in vascular volume, there is an ugly and controversial falling from grace for these compounds. In particular, they have been clearly associated with worsening renal outcomes in critically ill humans in a couple of VERY large and well-regarded studies (Lichtenstein

2014). They have also been shown to impact renal outcomes in a much smaller and more limited retrospective assessment of dogs (Hayes 2016). And lastly, the belief that the colloid molecules remain within the blood vessels has been called to question, and there is a growing concern that these molecules enter the interstitium, providing a colloid draw into the organs instead. (Woodcock 2012). If this is the case, they will worsen edema, increasing the diffusion distance for oxygen and metabolic byproducts, and helping to explain the evidence for worsening renal outcomes with their use. While providing adequate renal afferent volume and pressure remains intrinsic to renal auto-regulation and protection during anesthesia and surgery, it is beginning to look like colloids should not be part of the formula for achieving this. When isotonic fluid loading reaches the limits described above, a greater reliance will need to be placed on managing vasomotor tone, cardiac contractility, and the use of feline-specific blood products.

Inserting Additional Management of Homeostasis

While anesthesia tenants are generally the same across most disease states (manage breathing, oxygenation, blood pressure, cardiac rhythm, etc.), there are a few items that pop up with renal cases, largely because the kidneys either manage these things, or are greatly influenced by them. First, that while modification of vasomotor tone (increasing vaso-motor tone in particular) is becoming far more common to assist with blood pressure and volume management in non-renal cases, there is remains concern with altering afferent arteriolar pressure in renal disease. Thus, increasing vasomotor tone is seldom done, and never done lightly. Secondly, it has been shown that all inotropic drugs increase renal perfusion. The previous invocation of dopamine for renal cases (to increase bloodflow via dopaminergic receptors, specifically) is now known to occur simply through increased cardiac output, just like other inotropic drugs like dobutamine and ephedrine.

Management of electrolytes (Na, K, Ca), phosphate and glucose balance falls more on the anesthetist in renal cases, as the damaged kidneys do not always regulate homeostasis properly. This is generally simple- and involves measuring these, and adjusting the fluid composition as needed to augment or reduce them. The same can be said for red cell mass, and transfusion to provide adequate oxygen delivery should not be avoided when hemoglobin becomes too low (for sure by 5 g/dL).

Lastly, diuretics may or may not play a role in the management of renal cases. Furosemide is an oxygen-requiring diuretic, and so is usually reserved for a critical situation, when adequate volume to the kidney is assured, but inadequate GFR (or urine production) is found. Of more universal application may be the use of mannitol, which can help reduce a tendency to glomerular edema, increase GFR, scavenge free-radicals and increase blood volume transiently. When mannitol is elected for this purpose it is generally given at 0.1gm/kg/hour. When this is done, it becomes more important to manage volume status and fluid support in the post-operative period due to ongoing diuresis as the mannitol is cleared from the body.

Updates in pharmacology

Feline-friendly pharmacology has blossomed in the last couple of decades, greatly increasing the data-base for anesthetic and analgesic drugs that can be safely used in cats. Most of opioids have now been shown to have efficacy for treating pain in cats, and their MAC reducing qualities are vital in the safe management of renal patients. While peri-operative opioids should be selected from the mu-agonist category to maximize the analgesia, and thus anesthetic-sparing qualities of the opioids, there are also improved options for post-anesthetic opioid management with the addition of long-acting buprenorphine formulations (Simbadol), and the promising data for the efficacy of tramadol in cats. (Montiero B 2017) Likewise, there are now established NSAID choices in cats (Meloxicam, Robenacoxib) which will be discussed for post-procedure use below. However, in renal patients, the benefit of using an NSAID prior to, or during a procedure is complicated by the reduction of bloodflow that can occur secondary to the prostaglandin reducing effects of NSAIDs. Therefore, their use does need to be limited to the post-anesthesia period, when blood pressure stability is confidently anticipated to remain within normal limits.

Alfaxalone is the second major “gift” to feline anesthesia in the last decade. Sparing of cardiovascular function, and no more damaging to respiratory than other induction drugs, alfaxalone has provided an effective and more predictable alternative for anesthetic induction in cats when given IV after appropriate pre-medication/sedation. While no anesthetic drug is perfect, alfaxalone is quite good in this capacity. Problems tend to occur only when premedication/sedation are inadequate, or when the off-label IM route is used in fractious cats- where the drug becomes less predictable in terms of both efficacy and recovery quality.

The third major improvement in feline-friendly pharmacology is the approval of long-acting liposomally-encapsulated bupivacaine (Nocita) for use in cats. The first three days post-operative are the most painful, and long-acting local blocks that are accurately placed fill a huge need in the post-operative control of pain. Cautions exist for all drugs, but of concern for Nocita is adequate infiltration technique, and growing concern for use in head and neck procedures as there have been cases with loss of adequate oro-pharyngeal function. The only approved use of nocita in cats is based on declaw studies, so attention to off-label expansion of these uses to head and neck should be done with caution.

Quotes from: Montierro-Steagall, et al. Journal of Small Animal Practice 2019 May 12. doi: 10.1111/jsap.13012
Long-term use of non-steroidal anti-inflammatory drugs in cats with chronic kidney disease: from controversy to optimism.

Non-steroidal anti-inflammatory drugs (NSAIDs) are excellent analgesics administered as a single agent or as a component of a multimodal treatment along with other pharmacological and non-pharmacological therapies (Mathews et al., 2014). These drugs are the mainstay of treatment of several long-term painful conditions that are caused, at least in part, by inflammation. Nevertheless, they have narrow safety margins and can cause adverse effects including gastrointestinal, hepatic, renal and coagulation disorders (Monteiro-Steagall et al. 2013).

In cats, chronic kidney disease (CKD) is common, and has an unclear aetiology (Marino et al., 2014; Sparkes et al., 2016). Its prevalence increases with age and can affect up to 40% of cats over 10 years of age and 80% of cats older than 15 years of age (Marino et al., 2014). Osteoarthritis (OA) is the most common chronic painful condition in cats. Radiographic evidence of OA has been reported in as many as 61% of cats older than 6 years and in up to 90% of cats aged >12 years (Hardie et al. 2002; Lascelles et al., 2010; Slingerland et al., 2011). Other chronic painful conditions (e.g. cancer and periodontal disease) are also common in older cats. Painful conditions and CKD often co-exist in our feline patients and providing pain relief becomes a challenge due to the fear of NSAID-associated adverse effects. However, without treatment there are negative effects on feline welfare and quality of life. CKD may co-exist with OA in almost 70% of cats (Marino et al., 2014) yet, NSAIDs have historically been believed to be contra-indicated in cats with renal disease (Lascelles et al. 2005). Recent literature has challenged this belief and suggests that NSAIDs can, with care, be administered to cats with CKD. This capsule presents the current evidence and recommendations on the long-term use of NSAIDs in cats with CKD. (Monteiro-Steagall et al. 2013)

…Long-term NSAID therapy was found safe and efficacious when administered to cats with OA (mean age: 12.9 years old) for approximately 6 months. In this prospective study, no difference in serum creatinine levels were found between cats treated with meloxicam or placebo (n = 40 cats per group) (Gunew et al. 2008). Following their findings, investigators set out to discover if the previously reported safety profile of NSAIDs would be reproducible in cats with CKD. Results from two additional retrospective studies with meloxicam and one prospective study with robenacoxib indicate that NSAIDs can be safely administered to cats with stable CKD. The definition of 'stable' CKD is not clear in the literature. Some authors defined stable CKD as minimal changes in body weight and creatinine over time (less than 10–15% during 1 to 2 months) as well as controlled concurrent conditions such as hypertension, urinary tract infections and periodontal disease (Gowan et al., 2011, 2012). Other authors have considered changes in plasma creatinine concentrations greater than 25% over 1-2 months consistent with unstable CKD (Geddes, Elliott & Syme, 2013).

Recommendations for the long-term therapy of NSAIDs in cats with CKD

It is important to highlight that not all cats with CKD are good candidates for long-term NSAID administration. The ISFM has published extensive guidelines on this subject (Sparkes et al., 2016)

- *Stable CKD. For example, a stable patient with minimal changes in body weight and creatinine over time and controlled concurrent conditions including hypertension.*
- *The safety of NSAID therapy in cats with advanced CKD remains unknown. Most available studies have reported long-term NSAID therapy in IRIS stage 1 and 2 cats. Cats in IRIS stage 3 have also been treated but much less commonly.*
- *Long-term maintenance of hydration. Free access to fresh water should be provided at various locations around the house. Wet food also helps to increase water intake.*
- *The lowest or minimal effective dosage should be used based on response to therapy. The dose can be titrated downwards or upwards by the owner according to their observations of the cat's behaviour in the home environment. For OA, response to therapy includes increased level of activity and ability to perform activities (e.g. jumping, grooming, using the litter box), improved demeanour and socialization.*
- *General guidelines for management of CKD including phosphate control should be followed.*
- *The risks and benefits of therapy should be thoroughly discussed with the owners with a goal of improving quality of life.*
- *Owner education and involvement is paramount. Owners are part of the healthcare team since they will be administering treatments and monitoring clinical benefits and adverse effects. The latter include weight loss, decreased appetite, vomiting, polyuria and polydipsia.*
- *Ongoing monitoring should be performed via routine health checks including changes in body weight, body condition scores and blood pressure, and clinical pathology tests such as haematology, serum biochemistry profile and urinalysis. There is no gold standard of when and how often these should be performed.*
- *Environmental enrichment techniques should always be applied in the management of chronic pain in cats. Additional non-pharmacological techniques including physical therapy, acupuncture, nutraceuticals and chondroprotective agents might also be used even considering that the level of evidence for these techniques is low.*

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Veterinary Technician's Role in the Feline Healthy Wellness Visit

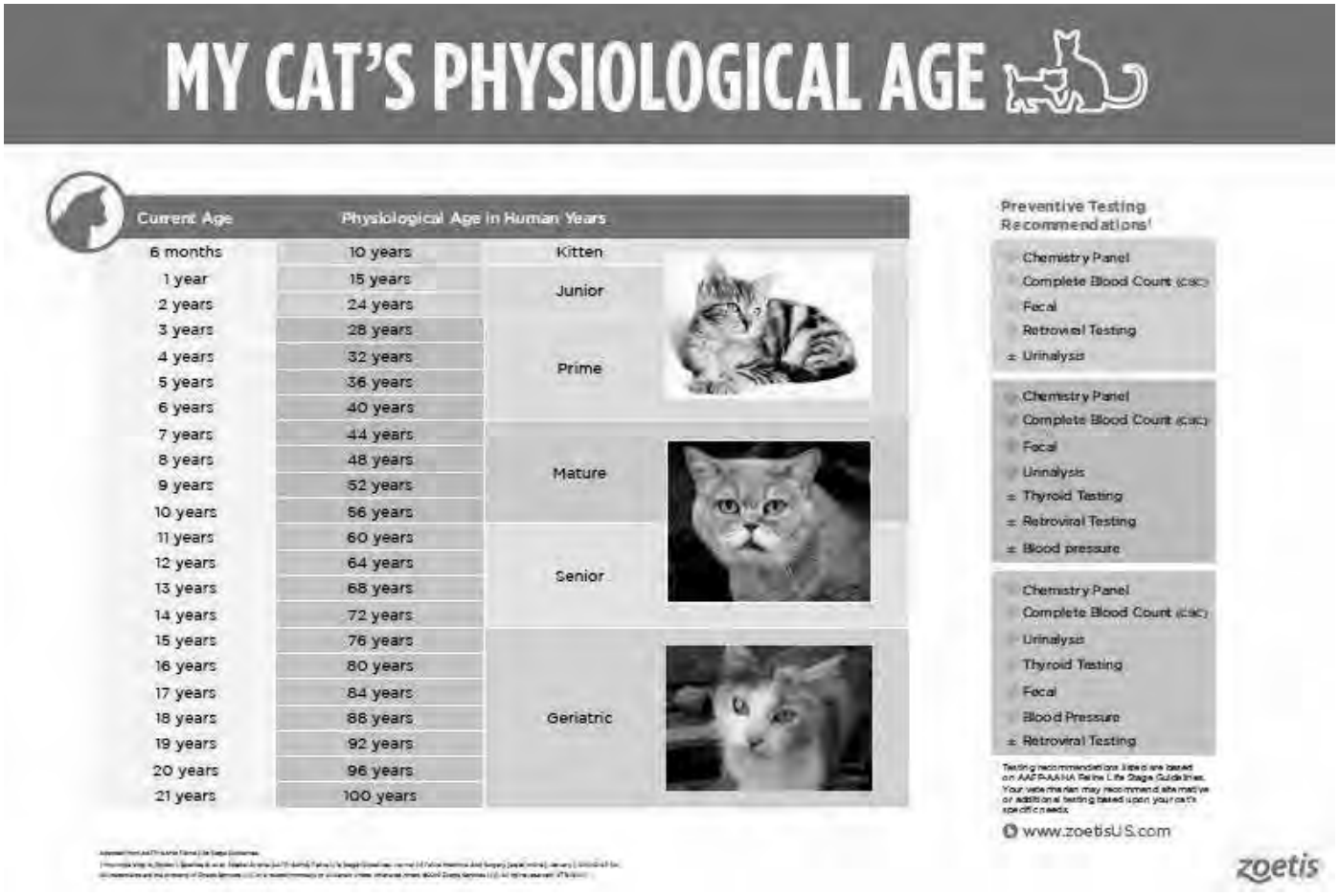
Rachel Poulin, RVT, VTS (SAIM)

Introduction

It is well established in both human and veterinary medicine that periodic wellness examinations represent best medicine, increase longevity, quality of life, are cost effective for the owners and are practice builders for the veterinarian. No-where in veterinary medicine is this truer than in feline medicine. Since in many cases it is the veterinary technician who has the most face time with a client brining in a kitten or a new cat for the first time it is often up to him or her to convey the value of wellness visits and provide the necessary information to help ensure owner compliance. It is also often up to the technician to demonstrate to the client the cat friendliness of the practice and to dispel the myth that bringing an apparently healthy cat into the veterinarian is somehow not worth the stress on the cat and client alike.

Wellness visits include a thorough history taking, physical examination, diagnostics, vaccinations, and discussions around administration of preventatives such as heart worm preventative, flea & tick preventatives and deworming for intestinal parasites. This lecture will focus on will laying out a recommendation for the diagnostics that should be performed as part of wellness and the reasons for recommending each test

See figure below for comparison between feline and human physiological age and age-based testing recommendations



The Details of age-based testing:

The minimal data base

The minimal data base is recommended at least annually for every cat of every age. It includes

- **A chemistry panel** including at the minimum screening tests for
  - Kidney disease – BUN, creatinine
  - Liver disease –
    - Liver function tests
      - BUN, glucose, albumin, ± bilirubin and cholesterol
      - Liver enzymes as markers for liver damage or inflammation – ALT, ALP ± GGT
  - Protein status
    - Albumin
    - Globulin
  - Endocrine disease
    - Glucose
    - Electrolytes
  - Electrolytes – sodium, potassium, calcium ± chloride
- **A complete blood count** including
  - Red blood cell parameters
    - Hct, MCV, RDW
  - White cell parameters including a 5 point differential
    - Total white cells
    - Neutrophils
    - Lymphocytes
    - Eosinophils
    - Monicytes
    - Basophils
  - Platelet count
- **Urinalysis** – A full urinalysis must be part of every minimal data base
  - Urine chemistry (dip stick)
  - Urine specific gravity (refractometer) - crucial to assess kidney function
  - Urine sediment evaluation (manual or automated) for
    - WBCs/ RBCs or other cells
    - Crystals
    - Bacteria
    - Casts
- **Fecal examination** – should be done for intestinal parasites at-least annually including in door cats
- **Heartworm testing** - should be done annually thru-out the United States including in door cats
  - Antigen and antibody screening is ideal

Additional Age Based Testing Recommendations

- **Retroviral testing** for FIV and FeLV – should be done in every kitten per AAFP guidelines and then in every adult cat with risk of exposure as part of the wellness examination
- **Thyroid screening** including palpation of the neck and T4 testing should be done annually in every mature cat (age 5-6 and up). This is crucial to identify feline hyperthyroidism early before it causes cardiac disease, hypertension etc.

Blood pressure monitoring and imaging can also be recommended in every mature cat for the early diagnosis of hypertension, neoplasia etc.

NOTES:

Diabetes & the Role of the Technician in Disease Management

Rachel Poulin, RVT, VTS (SAIM)

Diabetes Mellitus

Diabetes Mellitus (DM) is a common endocrine disease in cats. It is estimated that up to 1 in 400 cats are affected by DM[1]. DM is characterized by lack of insulin production or an insulin resistance. Without insulin the cell will no longer be able to utilize it for glucose and fuel. The lack of insulin can result in increased glucogenesis, glycogenolysis, lipolysis, and ketogenesis. Factors that can predispose a cat to DM include obesity, advancing age and males are more susceptible than females[2].

The Pancreas

- The pancreas has two main functions:
    - The exocrine pancreas aids in digestion
    - The endocrine pancreas produces hormones such as insulin and glucagon
        - Alpha cells produce glucagon which raises blood glucose levels
        - Betas cells produce insulin which lowers blood glucose levels
            - In both dogs and cats DM is caused by loss or dysfunction of pancreatic beta cells
            - In the cat, loss or dysfunction of beta cells is usually the result of insulin resistance, islet amyloidosis, or chronic pancreatitis[3].

Clinical Signs

- Common Clinical Signs of diabetic cats
    - Polyuria and Polydypsia
    - Polyphagia
    - Weight Loss/Muscle Wasting
    - Lethargy
- More severe clinical signs
    - Ataxia
    - Vomiting and Diarrhea
    - Hyporexia

Diagnosis

- Diagnosis is based on:
    - Clinical Signs
    - Confirmation of hypoglycemia and glucosuria
- Stress complications in cats:
    - Stress hyperglycemia can result in a false positive hyperglycemia
    - Further diagnostics will be required to confirm diagnosis
        - Confirmation of persistent hyperglycemia
            - Fructosamine
                - Protein that binds to glucose and gives reading of glucose levels of the last 2-3 weeks
                - Hemolysis can falsely elevate sample[4]
        - Rule out other causes of hypoglycemia and glucosuria
            - Hyperthyroidism
            - GI Disease
            - Endocrinopathies
            - Medication induced glucosuria
            - Kidney disease

Nutrition

Studies have shown that a low carbohydrate diet in conjunction with good glycemic control increases the likelihood of diabetic remission[5]. With diet and insulin therapy up to 60% of cats can enter diabetic remission[7]. Remission rates increase in cases with good glycemic control within 6 months of diagnosis[7].

Low carbohydrate (CHO) diets lead to decreased postprandial hyperglycemia and increase insulin concentrations leading to improvement of remission rates, improved clinical control, and decreased insulin needs.

Obesity leads to insulin resistance and glucose intolerance. Overweight cats should be fed a restricted energy diet to lose no more than 1% of body fat per week[9]. Rapid weight loss in felines can result in feline hepatic lipidosis (FHL)[10], a serious and potentially fatal condition. Therefore, diet and slow managed weight loss are imperative when treating feline diabetes.

Complications

Ten percent of cats with chronic hyperglycemia will develop diabetic neuropathy[13], resolution of this neuropathy is possible in time with good diabetic control, but resolution is not guaranteed. In addition, DM suppresses the immune system and makes fighting infections challenging for the patient. Skin infections and urinary tract infections are not uncommon developments for patients with DM. To make matters worse, an infection can cause inflammation and stress on the body that further deregulates diabetic control. Moreover, DM reduces the body's ability to heal. Therefore, if the diabetic patient were to sustain an injury or undergo surgery the recovery time would be prolonged and potentially complicated. For these reasons, and more, it is necessary to offer a very good diabetic education to the client, they should be able to know what warning signs are for a potential crisis and they should be aware of what risks this disease carries with it and why excellent control is so important on many different levels.

Communication/Empowerment and Tools

As stated before, DM is an overwhelming, complicated and expensive disease. The euthanasia rate for diabetic patients is 40%[13]. However, when a client is given the tools and education necessary to take care of their sick pet, when someone can offer them time, patience and knowledge of the disease, then the clinical team can greatly increase that patient's chances of survival. A diabetic patient can live a long and happy life when three factors all come together: 1) client compliance, the understanding and willingness to play a role in treatment, 2) the veterinary team's knowledge and ability, 3) patient response. It will not be possible to prevent every diabetic death; there are far too many complications and potential crises associated with this disease, but when all three factors come together we can increase quality and quantity of life for the patient and the client.

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NOTES:

Fluid Therapy

Ann Wortinger, BIS, LVT, VTS (ECC, SAIM, Nutrition), FFCP

Fluid Distribution
Fluids are distributed throughout various areas of the body, they can be found in the "extra cellular space" as with the blood and interstitial fluids, the "intracellular space" within the cells, and the "transcellular space" as with the cerebral spinal fluid, synovial fluid, lymph, bile, glandular and respiratory secretions and the gastrointestinal contents.

These fluids are maintained in a state of balance by the skin, lungs and kidneys working together. When there is a breakdown in this coordinated effort, then dehydration or hypovolemia can occur.

The body can obtain fluids by three routes, through oral intake (drinking), fluids contained within the foods that are eaten and water produced by the body from oxidation of carbohydrates, proteins and fats. They can be lost through "sensible losses"-those that are measurable; urine, stool, wound drainage and vomiting. "Insensible losses" are those that are unmeasurable or unseen; perspiration and respiration.

Indications for Fluid Therapy
Fluid therapy should be seen as a supportive treatment, if a disease process is causing the dehydration or a situation is present that is causing hypovolemia these need to be addressed and corrected for the fluid therapy to be effective. Intravenous fluid therapy can also be used during anesthesia and surgery to provide emergency venous access, and to help maintain adequate renal profusion and diuresis.

Dehydration is when the fluids in the body decrease causing an increase in the concentration of the solutes in the blood. This increase in solutes increases the osmolality of the blood resulting in fluids being pulled from the cells by osmosis (the movement of particles from an area of low concentration (outside the vessels) to an area of higher concentration (the blood) until the osmolality is equal). Dehydration can be caused by diarrhea, vomiting, anorexia, fluid loss through draining wounds, increased respiratory loss, fever, and diureses as with Diabetes Mellitus or chronic renal failure.

Hypovolemia is the loss of fluid and solutes from the extracellular space, either the interstitial or intravascular spaces. This loss can result in hypovolemic shock when there is insufficient blood volume to adequately perfuse the kidneys, liver, brain and heart. This loss can be caused by excessive bleeding, 3rd space shifts, Diabetes, fever, chronic renal failure, pleural or peritoneal effusion.

Goals of Fluid Therapy
The goal of fluid therapy is to increase tissue perfusion, replace fluid deficits, supply maintenance fluid needs and replace ongoing losses. To do this you need to be able to access the fluid deficits, calculate the maintenance requirements and estimate the ongoing losses. You also need to determine any electrolyte deficits that may exist and how best to correct these.

Assessment of Dehydration/ Hypovolemia
Percent dehydration-clinical signs

<5%-history of fluid loss with no clinical signs
5-6%- subtle loss of skin elasticity
6-10%- slightly prolonged capillary refill time (CRT), definite delay in skin return, +/- dry mucous membranes, and mild tachycardia
10-12%-dry mucous membranes, skin tents easily, definite delay to CRT, sunken eyes
12-15% tachycardia, weak, thready pulse, cool extremities, hyperemic dry mucous membranes, shock

On physical exam keep in mind that older pets may lose skin elasticity giving the impression of tenting when in fact it's normal. Obese animals may have normal elasticity and skin tenting even when dehydrated, and 3rd space fluid loss may not have any weight losses. 3rd space losses are fluids that accumulate within the body cavities or tissues (i.e. pleural or peritoneal space, gastrointestinal tract, edema, tissues around fractures or trauma sites).

Laboratory Findings
If possible, all blood work should be collected prior to fluid therapy. The PCV/TS will be elevated with all types of fluid loss except hemorrhage, then it would be decreased. The urine specific gravity will be increased (>1.045) with dehydration if renal function is normal, it will return to the isosthenuric range when rehydration is achieved.

Calculating Hydration Deficits
Estimate the hydration deficit, and convert the current weight to kilograms:
% Dehydration x body weight in kilograms=deficit in liters
Example: a 5# (2.27 kg) cat is 10% dehydrated
.10 x 2.27= 0.227-liter deficit
For shock, calculate the deficit in liters and multiple by 2-4, administer in ¼ increments, reassessing after each quarter.

With chronic disease, calculate the hydration deficit and either administer over a 4-8-hour period followed by the maintenance requirement or add maintenance requirement to the hydration deficit and administer over 24 hours.

Calculating Maintenance Requirements
Maintenance fluid and electrolyte requirements parallel kilocalorie requirements, with normal daily losses including respiratory, urine and fecal. Keeping this in mind maintenance fluid requirements can be calculated using: 40-60 ml/kg/

Comfort level and experience will dictate which number is used. These are fluid need estimates, if the animal indicates that it needs more or less fluids adjust accordingly.

Contemporary (ongoing) Losses
This is fluid loss that continues after fluid therapy has been started and would include losses from vomiting, diarrhea, polyuria, panting, large draining wounds, peritoneal/pleural fluid loss and surgical blood loss. If possible, these amounts should be estimated and added into the replacement fluid volumes. For surgical blood loss, 3 ml of crystalloid solutions should be given for each 1 ml lost. Once the condition causing the fluid loss has been corrected, the ongoing losses can be removed from the fluid volume estimate.

Calculating Replacement Rates
The rate of delivery will be dictated by the magnitude and severity of the loss. The maximum rates to be given safely would be: feline 50 ml/kg/hr. When giving fluids as a rapid bolus, monitor cardiac and renal function closely. If possible, fluid deficits should be replaced prior to anesthesia, then maintained at an anesthetic fluid rate of 5-10 ml/kg/hr.

To calculate the replacement fluid rate, you need to find the hydration deficit, the maintenance amounts and add in any ongoing losses. Add these three numbers together to get the replacement amounts. Administer 80% of the calculated replacement amount over the first 24 hours. This will allow the fluids to re-equilibrate within the body's fluid spaces, without a fluid over load. Example: A 10# cat presents 8% dehydrated. PCV is 37%, urine specific gravity is >1.040. She is vomiting approximately 10 ml every 2 hours.

What would be the hydration deficit? _____
What would be the maintenance amount? _____
What would be the ongoing losses? _____
How much/hour should be administered? _____

Hydration deficit: .08 x 4.5 kg=. 36 liters
Maintenance rate: 40-60 x 4.5 kg= 180-270 ml (.18-.27 liters)
Ongoing losses 10 ml every 2 hours=5 ml/hr
Total amount needed: 80% (.36+.27) =.63 liters/day=630 ml/24 hr +5 ml/hr=31.25 ml/hr

Fluid administration sets are available in adult and pediatric sizes. The adult size is typically 10 drops/ml (10 gtt/ml), the pediatric set is typically 60 drops/ml (60 gtt/ml). Check your individual sets, some are different.
To calculate the drops/min: Adult set-amount ml/hr divided by 6= drops/min
Pediatric set- ml/hr= drops/min

Routes of Administration
The route of administration depends on the clinical disorder and severity of signs.

Oral (PO); The most physiologic route, useful for hypertonic solution with a high caloric density. Not useful with gastrointestinal disease or dysfunction (i.e. megaesophagus), inadequate for acute or extensive loss.

Sub cutaneous (S Q);
Able to be done at home by owners, maintenance fluids amounts only. Not adequate for acute or severe loss. Only able to use isotonic solutions, do not add dextrose. In cases of shock or dehydration isotonic solutions are not absorbed from the SQ space due to decreased peripheral perfusion. If the fluids are not absorbed within 6-8 hours, or are transferred to the dependent sites (legs, belly, brisket), switch to IV use.

Intraperitoneal (IP); Allows for rapid infusions of large amounts of isotonic fluids.

Interosseous/Intermedullary (IO/IM); Useful in young or small animals where venous access may be a problem. Rapid dispersion of fluids via the bone marrow sinusoids and medullary venous channels.

Intravenous (IV); Allows peripheral and central catheter placement. Isotonic fluid administration through peripheral and central veins and hypertonic fluid administration only through central veins. Useful for emergency and surgical use, severe disease and acute fluid loss. If properly maintained, peripheral IV catheters can remain useful for 3-5 days, and 5-7 days with central catheters.

Fluid Types
Fluid types are based on plasma osmolality, for dogs this is ~300 mOsm/kg, for cats it is ~ 310 mOsm/kg.(1) Therefore an ISOTONIC solution would have the same osmolality as plasma or extracellular fluid. This would be called a "balanced solution", examples would be Lactated Ringer's solution, plasma, 0.9% NaCl or Normosol. A HYPERTONIC solution would have an osmolality > 300 mOsm/l. An example would be 7.5% NaCl. This type of solution can be used to draw fluids from the intracellular space to the extracellular space as a treatment for shock. This can lead to an intracellular "dehydration" adversely affecting the cellular function. Use of hypertonic fluid therapy can reduce the risks of pulmonary edema from high fluid administration. The duration of action is relatively short (< l hour), can produce a hypertonic state within the body and can result in a rebound interstitial edema. HYPOTONIC solutions are those with an osmolality < 300 mOsm/l. An example would be 0.45% NaCl. Because of their relatively low osmolality these fluids quickly move out of the vascular space.

MAINTENANCE CRYSTALLOIDS are solutions that are isotonic to plasma, with sodium (Na+) acting as the primary osmotically active particle. Only 25% of the administered amount remains within the vascular space after 1 hour. These solutions contain electrolytes and nonelectrolyte solutes and are able to enter all of the body fluid compartments. Electrolytes are those substances that, when in solution separate into electronically charged particles called ions. The positively charged ions are called "cations" and are: sodium (Na+), potassium (K+), calcium (Ca+) and magnesium (Mg+). The negatively charged ions are called "anions" and are: chloride (Cl-), phosphorus (PO4-) and bicarbonate (HCO3-). Crystalloids can be used to expand the vascular space but 2.5-3.0 times as much must be used when compared to colloids, this is because of their ability to redistribute to the extravascular spaces. These can be classified as either replacement fluids (i.e. LRS or Normosol), or maintenance fluids (fluids with lower Na+ and higher K+ than replacement fluids).

COLLOIDS are solutions with large sized particles that can be used to expand the vascular space, and having little effect on the intracellular spaces. Particle size affects the length of time that the particles remain in the vascular space, the larger the particle the longer the time. These solutions can be useful in cases of shock where vascular volume expansion is needed, in cases of severely low serum albumin levels (<1.5 mg/dl) or situations where risk of edema is high. Colloids are available in natural and synthetic solutions. The synthetic colloids, Dextran 40 & 70 (denotes particle size) and Hetastarch are helpful for volume expansion and promotion of peripheral blood flow, but only 20-30% of the administered volume is still within the vascular space after 24 hours. Because of their large particle size, for each gram of Dextran or Hetastarch administered, 20-30 ml of fluids are "pulled" (by osmosis) from the intracellular space.

Natural colloids would include albumin, fresh frozen plasma (FFP) and whole blood. Plasma, if prepared properly is stable frozen for 2-5 years and contains the proteins albumin and globulin. FFP and fresh plasma also contain active clotting factors and platelets. Whole blood is useful for anemia and severe hemodilution. Packed red blood cells (whole blood that has had the plasma volume removed) may be more appropriate than whole blood for treating anemia. The plasma in the whole blood will act as an osmotic colloid and pull additional fluid into the vascular space, where if pRBC's were used and reconstituted with 0.9% NaCl (an isotonic solution) this would not happen.

Hypervolemia
Over hydration can occur when fluids are administered too rapidly or retained improperly. This can cause the appearance of a serous nasal discharge, restlessness, moist cough, dyspnea, edema, pulmonary crackles, ascites, polyuria or exophthalmos. The PCV would become lower and the body weight would go up. Some of the physical conditions that could cause hypervolemia would include, congestive heart failure, anuric renal failure, steroid administration and decreased dietary protein intake.

When to Stop!!

Ideally when the hydration deficit has been corrected, the fluid rate would have been decreased to the maintenance amount plus ongoing loss, when the ongoing losses have been stopped the fluid rate would have again been decreased to the maintenance amount. When the animal is able to drink and hold down water, the fluid rate should again be decreased by 25-50%. By stepping down the fluid rate slowly, the body is allowed adequate time to adjust to the shifts in fluid volumes within the body. This can also help to prevent hypervolemia.

NOTES:

Nutritional Management of Patients with Vomiting & Diarrhea

Ann Wortinger, BIS, LVT, VTS (ECC, SAIM, Nutrition), FFCP

Introduction

One of the most important things to remember when dealing with a patient with vomiting or diarrhea, is that neither of these are in themselves diseases, but rather signs of disease. There are few clinical studies that have evaluated specific dietary manipulation on either the prevention or management of gastrointestinal disease in cats. To date we have no physical test finding, lab test results or historical facts that are predictive of which feeding method will be most effective in managing signs in a particular patient, even with a definitive diagnosis individual feeding trials and routine follow-up visits with the veterinary team are essential in managing these signs. If there is no improvement in clinical signs over a 2-3-day period for acute vomiting or diarrhea or if the patient continues to deteriorate despite treatment, reassessment is necessary.

Causes of Vomiting

Vomiting can be causes by any number of things, not all of which are related to the stomach. Vomiting can be induced with motion sickness, ingestion of emetogenic substances, gastrointestinal tract obstruction, abdominal infection or inflammation or extra-gastrointestinal diseases that stimulate the chemoreceptor trigger zone. The most important clinical sign of chronic gastric disease is vomiting.

The dietary behavior and lifestyles of carnivores, such as cats, are such that occasional vomiting is not considered clinically significant especially when the vomitus is mixed with hair. In cats specifically, vomiting can be seen as a sign of a more distal intestinal disorder, even in the absence of other clinical signs.

Causes of Diarrhea

Diarrhea is a non-specific sign of many diseases, and effective management will depend on identification of the underlying cause, and resolution or removal of this cause if possible. Acute diarrhea is most typically caused by dietary indiscretion or intolerance, intestinal parasites and infectious diseases such as *Salmonella* or *E.coli*. Chronic diarrhea is most commonly caused by intestinal disease, though other systemic diseases may affect intestinal function and can induce secondary hypersecretion or intestinal malabsorption. The most common cause of chronic vomiting and diarrhea in cats is caused by the constellation of diseases found under the heading of inflammatory bowel disease.

Acute diarrhea can often be treated symptomatically and will resolve within 2-3 days with minimal treatment. Chronic diarrhea is rarely self-limiting, with treatment being based on definitive diagnosis.

To Withhold Food or Not

For years our standard treatment for acute vomiting or diarrhea has been to withhold food for 12-48 hours. The belief has been that by removing food from the already upset GI tract we could allow it to clear itself of luminal contents that may be causing the problem, to help prevent mucosal cell abrasion by the GI contents, deprive the opportunistic luminal bacteria of nutrients preventing proliferation, preventing absorption of dietary antigens that may be present due to maldigestion and to permit restabilization of the brush border enzyme function. The problem with this approach is that in almost all cases of enteritis, regardless of the cause, there is a decreased motility with delayed gastric emptying and reduced segmental contractions. Therefore, fasting would not immediately provide any physical rest for clearing for the GI tract.

Studies in human patients have shown that early reintroduction of feeding resulted in shorter time for the return of gut sounds and a trend towards shorter hospital stays. Evidence also suggests that the prokinetic effect of feeding may decrease the vomiting response in some patients. We know that oral fasting alone can induce an intestinal insult, with mucosal atrophy occurring within 12 hours of a fasting state. While it may be easier to convince clients to continue to feed a patient with diarrhea, it is unlikely a client will continue to feed an animal with vomiting

Treatment Options

The primary goal for management of vomiting or diarrhea is to maintain delivery of nutrition to the GI tract, prevent nutrient deficiency and malnutrition. The most common first step is introduction of a highly digestible, low fat diet. Many times, we will recommend that the patient be started on small amounts of a bland diet. There is little evidence to support this recommendation, and the term ‘bland’ is poorly defined and vague. With any inflammatory process in the GI tract, the type of diet offered is more important than the ‘blandness’ of the ingredients. Diet selection should be based on the specific disease being treated, the area of the GI tract that is affected and the ability of the diet to promote tissue healing and maintain remission of clinical signs.

Our long-term goal in management of vomiting and diarrhea is to help repair the damaged GI tract lining, restore normal GI bacterial populations, to promote normal GI motility and function, to support the immune system and decrease GI tract inflammation. An animal with chronic vomiting and diarrhea with subsequent loss of nutrients and energy may present with weight loss, poor hair coat, and dry flakey skin. These patients will respond well to a food with increased nutrient density in addition to the other nutritional modifications. As always, it is important to remind clients that when we provide nutrition to the debilitated patient, the body has the final decision on where those nutrients and where that energy is distributed to. We cannot decide that we want increased muscle mass when the body wants to replace intracellular protein and fat stores. Some clients may find this frustrating, but the body makes all the final decisions not the veterinary team. Our job is to provide the building blocks to rebuild the damage so the patient can achieve full recovery.

Adverse Food Reactions and Food Responsive Diarrhea

Food allergies in cats is seen as being uncommon, though some clinicians believe that they are more likely to occur with diets that are consumed during periods of acute gastritis as larger pieces of peptides are allowed to cross the intestinal barrier during these times potentially sensitizing the immune system. If an adverse food reaction is suspected, the current recommendation is to feed a highly digestible, single source novel protein diet. The thought being that a highly digestible diet has lower antigenicity because fewer intact proteins are absorbed across the inflamed intestinal barrier. The ideal diagnostic and long-term management of suspected cases is based primary on using novel proteins or protein hydrolysates and monitoring patient response. The initial use of a sacrificial protein may be recommended. This sacrificial protein may still develop some allergic response, but will allow the intestinal tract to heal. Once healing has been achieved, a long-term maintenance diet utilizing a different protein can be introduced.

Dietary management of these conditions can be difficult in practice because they are slow to respond, and the animals remain at risk for relapse if they gain access to the problem ingredient. A minimum trial of 3-4 weeks is recommended, though some clinicians will go for 3-4 months before making any diet changes.

Adverse reactions to food are more common than actual food allergies, and have been reported to be as high as 29% of all cases of chronic gastrointestinal disease in cats. Adverse reactions can be seen with lactose intolerance in adult animals as well as loss of digestibility to certain nutrients and development of flatulence with digestions of some fibers.

Gluten, specifically wheat gluten has received a lot of press lately with the advent of new, ‘grain-free’ and ‘gluten-free’ diets for pets. Gluten is a plant protein that provides an excellent source of amino acids. On average, gluten contains 80-82% protein, with low dietary fiber and a digestibility of approximately 99%. Gluten is also an important source of the amino acid, glutamine which has been shown to be important in maintaining digestive integrity and conserving lean muscle mass during intensive activity. Irish setters are the only breed of dog or cat in which gluten sensitivity has been documented. For these dogs a gluten-free diet would be recommended. Rice and corn do not contain gluten, where wheat, rye, barley and oats all contain gluten.

Protein

A protein source that is of high quality, easily digested and assimilated, and contains all the essential amino acids in the correct proportions would be recommended. Quality of a protein is measured by digestibility, as determined by feeding trials and by the biologic value of the protein. Biologic value (BV) is a determinant of the availability of the essential amino acids within a specific protein. The protein source with the highest biologic value is eggs with a BV of 100. Protein digestibility can vary between animals that are healthy as opposed to those who have disease, and can be affected by food processing methods. Dietary proteins also present the largest source of dietary antigens, and are recognized and responded to by the immune system.

Proteins in the diet are essential for secretion of hormones and enzymes required for digestion. This includes the release of the pancreatic enzymes as well as the hormones insulin, gastrin, cholecystokinin. Insufficient caloric availability in the diet, intestinal protein loss, increased catabolism and decreased absorption can all result in lower protein levels in the body. Minimum total diet digestibility of 85-88% dry matter (DM) are recommended with a protein digestibility of > 92%.

Fats

While fats are the most calorically dense nutrient and inclusion in the diets would benefit those patients who are malnourished, absorption of fats through the intestinal lymphatic’s may be impaired and could contribute to a postprandial increase of fluid influx into the intestinal tract further contributing to the development of secretory diarrhea. In cats, higher fat diets may be beneficial in slowing gastric emptying especially with diarrhea. The content is recommended to be ~ 11-15% DM or less of the diet.

The presence of the Ω-3 class of fatty acids has been found to be helpful in management of inflammatory responses in the body, including those occurring in the GI tract. Both Ω-3 and Ω-6 fatty acids are essential and therefore required in the diet, by manipulating the ratio of these two fatty acids; we can decrease the inflammatory response.

Carbohydrates and Fibers

Similar to proteins, carbohydrates should be easily digested and assimilated by the intestinal tract. The carbohydrate with the highest digestibility is cooked and blended white rice. Alternatives to rice would include potato, tapioca and corn. All of these should be blended or ground before feeding to break down the cellulose outer shell allowing to body to reach the nutrients within the cells. Many times, we will recommend cooked rice in a home-made diet, but the whole rice grain may pass through the entire GI tract relatively intact due to impaired ability to access the contents through the fiber shell. Blended rice or baby food flaked rice are more digestible than is plain cooked rice.

Fibers are useful in the management of GI disease, as well as maintenance of GI health. The type of fiber used as well as the level found in the diet is important. Those fibers that result in production of the short-chain fatty acid (SCFA) butyrate are preferred. Butyrate is the preferred energy source for the colonocytes, obtaining ~ 70% of their energy from luminally derived SCFA. Fibers can also increase peristaltic contractions, and may inhibit colonic contractions. SCFAs have been shown to protect intestinal tissue and promote restoration of normal intestinal function. The addition of highly fermentable fibers that produce high levels of SCFAs can cause diarrhea and flatulence and may interfere with the digestion and absorption of other nutrients.

Both soluble and insoluble fibers may be beneficial in symptomatic treatment of large bowel diarrhea by allowing modulation of water retention. Which fiber will be most beneficial may depend greatly on the patient's response to fiber inclusion in the diet, unfortunately, there is no one fiber fits all. Including highly fermentable fibers such as gar gum, lactulose and pectin, may actually increase the incidence of diarrhea, flatulence and may interfere with nutrient digestion and absorption.

Prebiotics

Prebiotics are specific short-chain carbohydrates usually classified as fibers based on their digestibility by the GI tract. Some of the more commonly available prebiotics include inulin, galactooligosaccharides (GOS), lactulose, fructooligosaccharides (FOS) and manooligosaccharides (MOS). The benefit to the intestinal tract of these specific fibers is their ability to be broken down by the intestinal bacteria with production of SCFAs and their ability to help modulate GI motility. Butyric acid or butyrate is one of the SCFAs produced that provides energy for the colonocytes and has been shown to have anti-inflammatory properties on the surrounding tissue.

The fibers used can also help modify the composition and metabolic activity of the GI bacteria, and allow the non-pathogenic bacteria to out compete the pathogenic bacteria allowing readjustment of small intestinal bacterial overgrowth. This occurs through changes in pH caused by the production of the SCFAs.

Probiotics

Probiotics are actual bacteria that are introduced into the GI tract with the intention of reestablishing a population of good bacteria and outcompeting the bad bacteria that may be contributing to the disruption of the GI tract. The most important thing with including probiotics in the diet is ensuring that they actually survive the stomach acid, the bile acids and are able to make it alive into the duodenum. Not all probiotics are created the same, and if they don't survive to arrive at the small intestines, you have just included a really expensive protein source in the diet. Look for actual feeding trials documenting the survivability of the specific strains of bacteria included in the product. Explaining to clients the advantages that veterinary specific strains of bacteria provided over what they can get OTC is also important.

Conclusion

Diet selection will be ultimately determined by the cause of the signs as well as individual patient response. There are many commercially available therapeutic diets that offer options for management of intestinal diseases including low fat, novel protein and modified fiber diets. As there are no physical test finding, lab test results or historical facts that are predictive of which feeding method will be most successful, individual response and follow up with the veterinary staff is necessary for optimal success.

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NOTES:

Refeeding Syndrome: Does it Really Exist?

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Introduction

A phenomenon has been noted in historical records in humans describing epidemics of death when starving people gained access to food. When allowed to engorge themselves, they became severely ill and died. Those people that did not engorge themselves but consumed small amounts of food did not suffer the same fate. (1) Not until the liberation of Holocaust victims in WWII where they able to identify the cause of death, and why this only occurred to those people overindulging. It was finally realized that refeeding small amounts of food or milk would prevent this disaster. (1). Even then it was not fully appreciated that overly aggressive refeeding could cause serious metabolic derangements. (1) Not until means to measure electrolytes levels in the blood were available was the exact cause of this derangement determined. (1) In human medicine this metabolic derangement is still seen with severe anorexia nervosa, chronic alcoholics, diabetic ketoacidosis or those having gone on hunger strikes. (1, 2)

More importantly to us in veterinary medicine, this metabolic derangement can also be seen in our patients. Typically, these patients present with a prolonged history of anorexia or other metabolic condition such as Diabetic ketoacidosis. (1, 3) When a body goes into a starvation situation, a complex set of changes or adaptations occur. By understanding these changes, we are better able to understand what happens when we start to “refeed”. (2) The metabolic rate slows down decreasing the energy necessary to run the basic needs of the body, in addition a reduction in the functional reserve of most if not all the organ systems occur. Significant reductions occur in cardiac output, hemoglobin level and therefore oxygen carrying capacity, renal concentration capacity, gastrointestinal villous atrophy and slowing of GI motility. (2) These reductions in functional reserves are not severe enough to cause failure of any one organ system during starvation.

In humans, potential complications of refeeding include generalized muscle weakness, tetany, myocardial dysfunction, cardiac arrhythmias, seizures, excessive sodium and water retention, hemolytic anemia and death from cardiac and respiratory failure. (2, 4) While seen rarely in veterinary medicine, it is seen most often in those patients receiving enteral or parenteral nutritional support. (4)

Clinical Presentation

Keeping in mind the changes the body has undergone while in starvation, when reintroducing food several areas need to be monitored closely to prevent the “Refeeding Syndrome”. During recovery, excessively rapid refeeding (or hyperalimentation) can overwhelm the patients already limited functional reserves. (2)

Refeeding causes a shift in the body from a catabolic state where protein is the primary energy source to an anabolic state where carbohydrates are the preferred energy source. (2, 5) Administration of enteral or parenteral nutrition stimulates the release of insulin; this causes dramatic shifts in serum electrolytes from the extracellular space to the intracellular space, primarily phosphorus, potassium and to a lesser degree magnesium. (2, 5, 6) Insulin promotes intracellular uptake of glucose and phosphorus for glycolysis. (5)

Prior to reintroducing food, the serum electrolyte levels are usually within normal ranges, and may even be elevated. (2, 4, 5) During catabolism as body cell mass shrinks, the intracellular ions, phosphorus, potassium and magnesium move in to the extracellular space. (2) From there they are excreted through the kidneys as they reach the renal threshold. This loss through the kidneys continues to happen even with continued depletion. (2)

During refeeding, these ions move back into the re-expanding intracellular space, and the serum levels can fall dangerously low within 24-72 hours. (2, 5) Treatment of uncontrolled diabetes with insulin can lead to identical electrolyte shifts. (2)

In addition to electrolyte abnormalities another potential problem is fluid overload. Because of the decrease in functional reserve in the heart and kidneys death from congestive heart failure is a possibility. If carbohydrates are reintroduced too quickly, the resulting fluid retention can overwhelm the patient’s limited cardiac reserve causing heart failure. (2) Carbohydrate intake stimulates the release of insulin, one of the actions of insulin in addition to regulating glucose is to reduce sodium and water excretion. (2, 6) Dextrose containing intravenous fluids can also cause the same problems without having food being given due to the rise in serum insulin levels driving the dextrose into the cells.

Those patients most "at risk" for developing Refeeding Syndrome are:

- Cats with hepatic lipidosis-the more severe the more "at risk"
- Diabetic Ketoacidosis
- Severe malnutrition/starvation
- Hyperadrenocorticism (Cushing's Disease (3)

Phosphorus

Phosphorus in the form of phosphate is the most abundant intracellular anion. (3,7) Most intracellular phosphorus exists as organic compounds, such as creatine phosphate, adenosine monophosphate (AMP), and adenosine triphosphate (ATP). (1) Organic phosphate is also present in many compounds in the body such as phospholipids, phosphoproteins, nucleic acids, enzymes, cofactors and biochemical intermediaries. (3) Phosphorus is involved in cell membrane integrity (the phospholipid layer), muscle and neurologic function, carbohydrate, fat and protein metabolism, oxygen delivery from the red blood cell (RBC) to the tissue, and the acid-base buffering system. (7) Phosphorus also aids in the transfer of energy to cells through the formation of ATP and is an essential component of bones and teeth. (7)

Most extracellular phosphorus is in the form of inorganic phosphorus, approximately 12-15% of this is protein bound, and the remaining 85-88% exists unbound as either monohydrogen phosphate or dihydrogen phosphate. (3, 7) Only inorganic phosphate ions are measured when serum is analyzed for the presence of phosphorus. (3) Serum should be separated from cells within 1 hour of sample collection; leakage of cellular organic phosphate into the serum may increase the inorganic phosphate concentration. Hemolysis can have the same effect. (3)

As with any ion found predominately in the intracellular space, serum concentrations do not represent total body stores. (3) Phosphorus normally shifts freely between the extracellular, intracellular and boney compartments. (3) Hypophosphatemia does not imply that phosphorus depletion exists; just that it has shifted out of the measurable extracellular space.

Phosphorus moves into the cells with refeeding to support the increased production of phosphorylated intermediary components of energy metabolism. Severe hypophosphotemia, hemolytic anemia and death can occur within 12-72 hours of refeeding.

Because of the phosphorus requirements for formation of ATP, signs of hypophosphatemia are often related to decreased energy stores and may include muscle weakness; anorexia, dysphagia and respiratory failure caused by decreased diaphragmatic contractility and decreased cardiac output. Decreased oxygen delivery to cells, depleted cell energy stores, seizures and coma may result. (7)

Severe hypophosphatemia may impair heart function by reducing the energy generating ability of the left ventricle. This is thought to be the result of depleted intracellular ATP stores and/or impaired calcium metabolism. (3) Approximately 20% of human patients show cardiac arrhythmias, even when underlying heart disease was not present. After repletion of phosphorus, the severity of the arrhythmias improved. (1, 3)

The red blood cell is the only tissue in the body that produces 2, 3-diphosphoglycerate (2, 3-DPG). 2, 3-DPG is bound to hemoglobin and helps to enhance dissociation of oxygen from the hemoglobin molecule. (1, 3) A deficiency of RBC 2, 3-DPG impairs release of oxygen from the hemoglobin molecule causing hypoxia. (1, 3)

Muscle contraction also requires ATP as an energy source, low concentrations of intracellular phosphorus results in depletion of these energy stores causing muscular weakness and respiratory failure. (3)

ATP depletion is also the proposed mechanism by which hypophosphatemia may cause hemolysis. ATP is needed to maintain RBC membrane integrity, cell shape and deformability. Glycolysis is the only means by which RBC's generate ATP. Decreased concentrations of inorganic phosphate therefore limit ATP production. ATP depletion may cause malfunction of the sodium-potassium pump, which causes decreased cell deformability and osmotic lysis. (5)

Phosphorus depletion can occur in the absence of hypophosphatemia in diabetic ketoacidosis. This is due to the effects of insulin on extracellular phosphorus and potassium and not necessarily due to the effects of "refeeding". Supplementation should be done in animals than have low normal or moderate hypophosphatemia prior to starting insulin therapy. Monitoring of serum phosphate is critical during the first 12-24 hours after starting insulin and fluid therapy. (1, 3)

Cats have low levels of hepatic glucokinase, the enzyme that phosphorylates glucose for hepatic use. This deficiency makes cats particularly susceptible to hyperglycemia when either fed diets high in glucose or receiving fluids containing

glucose. (5) This elevated serum glucose further stimulates the production of insulin, which causes an increased shift of phosphorus from the extracellular space into the intracellular space. (5) Enteral diets high in simple carbohydrates can have the same effect. (5)

Potassium

Potassium is the primary intracellular cation, with at least 90% of the total body stores located in the intracellular space. (7) Since potassium like phosphorus is located primarily intracellularly, serum levels often do not accurately represent the extent or severity of potassium deficiency, especially in cases of chronic disease. (7) Potassium has a direct impact on cell, nerve and muscle function by maintaining the cell's electrical neutrality and osmolality, aiding in neuromuscular transmissions, assisting skeletal and cardiac muscle contractility, and affecting the acid-base balance. (7)

Since potassium is an integral part of the sodium-potassium pump, hypokalemia usually results in muscle weakness and decreased GI motility. (7) An ECG will show prolonged repolarization (the period of time in which the Na+-K+ pump moves the potassium back into the cell and the sodium out), this causes a prolonged PR, QRS and QT intervals, a decreased ST segment and a flattened inverted T wave. When the deficiency is severe enough, sinus bradycardia and heart block with atrioventricular dissociation can be seen. (7)

Insulin also pulls potassium along with phosphorus into the intracellular space with resumption of carbohydrate metabolism. (2, 4) When potassium and glucose move into the cells with insulin, the Na+-K+ pump and glycogen synthesis is stimulated. This further depletes the body of potassium, since 0.33 mEq of potassium is required for each gram of glycogen produced. (4)

Magnesium

Magnesium is the second most abundant cation in the intracellular space. Approximately 60% of the body's magnesium can be found in the bones and teeth, 39% in the intracellular space and less than 1% in the extracellular space. (7) As with phosphorus and potassium, serum magnesium levels do not accurately reflect actual body stores because of the relatively small amounts found in the serum. Approximately 30% of the magnesium in the serum is protein bound; therefore reduced albumin levels may falsely decrease the serum reading even if actual levels are within normal limits. (7)

Magnesium promotes enzymatic reactions within cells during carbohydrate metabolism and helps the body produce and use ATP. (7) Signs of hypomagnesemia are similar to those seen with hypokalemia, respiratory muscle paralysis, complete heart block and coma. (7) Hypomagesemia also causes an inappropriately high excretion of potassium through the urine, thus making worse any existing hypokalemia. This occurs because sodium-potassium ATPase which is required for reabsorption of potassium is magnesium dependent. This also prevents correction of the hypokalemia even with high doses of potassium supplements until the hypomagnesemia is corrected. (2, 4, 7) Hypomagnesemia can also cause a secondary hypocalcemia, which remains resistant to supplementation until magnesium is corrected. (2, 4) This happens because with magnesium depletion, parathyroid hormone (PTH) is unable to elicit calcium release from the bone. Even though the body initially continues to secrete increased levels of parathyroid hormone to stimulate calcium release, the continued hypomagnesemia will eventually inhibit PTH secretion. (2, 7) A patient with hypocalcemia due to hypomagnesemia may have a high, normal or low PTH level. (2) Animals with hypocalcemia can show signs of restlessness, muscle fasciculation's, tetany and convulsions.

Recommendations for Avoiding Refeeding Syndrome

1. Anticipate the problem whenever a patient is "at risk" and refeed with formulations known to contain adequate levels of phosphorus, potassium and magnesium.
2. Use initial nutritional refeeding rates not to exceed the patient's resting energy requirements (RER) (30 x weight in kilograms) + 70. Consider refeeding a high-fat low carbohydrate diet to patients who haven't eaten in greater than 5 days, if their condition would not contraindicate such a diet.
3. Do not add extra energy to the caloric requirements by using an Illness Energy Requirement adjustment to the RER
4. Monitor phosphorus, potassium, magnesium and PCV/TS at least daily, more often if indicated. Monitoring should start within 12 hours of refeeding.
5. Supplement electrolytes as needed, either IV or with the food.
6. Monitor closely for signs of fluid over load and congestive heart failure. (2, 4)

Conclusion

The take home message here is to be aware, monitor and when feeding "go slow, go low". We have found that starting feedings at 25% of RER with continuous rate infusion with a syringe pump to be the best way to address this. We use recovery diets exclusively, and supplement as needed. Some diarrhea is not unexpected in patient's that have undergone prolonged starvation due to GI villous atrophy. It does no one any good to try and rush the feedings to get

the patient out of the hospital, especially if you create more problems that you already had!! If you've never seen a patient with refeeding syndrome, you haven't been looking in the right place. They're out there, and we need to find them so that they can be treated appropriately.

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NOTES:

Counseling Clients in Crisis

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Webster's defines a crisis as "a turning point in a disease for better or worse especially a sudden recovery, an intensely painful attack of a disease, a turning point in the course of anything; decisive or crucial time, stage or event, a time of great danger or trouble, whose outcome decides whether possible or bad consequences will follow".[1] Obviously, this leaves a lot of latitude in what we and our clients call a crisis. Basically, a crisis is whatever the client thinks it is.

A crisis can be precipitated by many things; financial concerns (how can I pay for this), concerns over the pets ability to fully recover, concerns over the course of the disease (how much longer will we have together), concerns over how to handle the end (euthanasia or hospice, burial or cremation, etc.), concerns over how to handle the recommended treatment (inability to orally medicate or administer SQ fluids or injections), concerns over how other pets in the house will treat the patient, concerns over how their friends or family will view the pet or treatment options.

The Human-Animal Bond

To be able to most effectively help our clients first we have to understand the bond they have with their pet. The stronger and more stable the owner's bond with the pet, the greater the owner's commitment to the animal and its recovery. The greater the owner's commitment to the pet, the greater the compliance. The greater the compliance, the greater the chance of success. The greater the success, the more readily owners justify the cost of any treatment and praise the clinician who formulated it, and finally the more serious the problem, the greater the influence of all these factors in an owner's decision. [2]

There is a vast continuum along the human animal bond with varying degrees of attachment seen. At the strongest or most attached end is the client that has an anthropomorphic attachment to their pet. This client tends to assign human qualities to their pet; this can result in a relationship with a great degree of emotion attached. [3] While this may be evident all the time with some clients, others may only display this when their pet is ill. [3]

A client with anthropomorphic attachment to their pet tends to pay very close attention to their pet and with a little effort it is possible to separate out what they think the animal feels from what is clinically relevant to the problem at hand. [3] When presenting information, remember they relate better to analogy than to linear fact. They want to know what they would be experiencing if they had a similar problem, not specific references to anatomy and physiology. [3] The down side to this attachment is if the client feels that they wouldn't do that treatment or use that medication on themselves, they won't do it on their pets-regardless of the clinician's opinion, or differences in physiology between humans and animals.

An anthropomorphic attachment can also lead to co-dependencies and separation anxiety in both the client and the pet; these problems become their most severe when a client is faced with a terminal illness or death of the beloved pet, not to mention the possibility of having to decide on euthanasia. [3] We as veterinary care professionals tend to be more anthropomorphic in orientation, though often not to the extent of some of our clients. This too will affect how we approach a case, and how we deal with our patients.

At the other end of the human animal bond spectrum are the clients that view their pets as chattel, or inanimate possessions. The primary distinguishing characteristic of this orientation is the lack of an emotional tie with the animal, for this reason we seldom see this in clients who have routine one-on-one contact with their pets. [3] The chattel orientation is most commonly seen among absentee owners, those whose animal is trained and handled by someone else, the status symbol pet who lives outside or those who have a large number of animals but no direct contact with any of them. [3]

An owner with a chattel relationship with their pet disavows the existence of the human-animal bond. Because market value and utility serve as the foundation, these people often maintain very clear ideas of what they will and won't do for the animal. While this orientation maintains objectivity when presented with a problem, we also lose a commitment to the animal's welfare. Unfortunately, we can't make these owners "care" about their pets, and in trying to do so we can waste a lot of time and energy that could be directed elsewhere.

Midway between these two approaches is the integrated orientation, these clients relate to animals neither as people nor objects but rather as separate animal beings who become incomprehensible beyond a certain point. [3] The good

part is that this orientation recognizes the animal as a unique and separate animate creature; the bad part is that these owners may place what we consider detrimental limits on the animal and its needs. Those owners who take the integrated approach establish a mental barrier that defines the limits of their relationship with a responsibility to the animal. When the animal crosses this border, the owners see the animal as independent of their influence. This, in turn, may lead the owner to emotionally and or physically abandon the animal to fend for itself. [3]These owners may hold the animal totally responsible for any behavior that violates their definition of normal or good. [3]

Communication-The Key

Once we have defined the type of relationship the client has with the pet, we need to discuss the implications of treatment as well as the anticipated result of these for both the owner and the pet.

Unlike human medicine, veterinary medicine has relatively few third-party payers (insurance). When insurance pays a portion of the bill, you never know what the anticipated total will be until the final bill arrives, and you're done arguing with the insurance company. For veterinary medicine, it is very important that clients are well aware of what kind of monetary costs they're looking at, and what the anticipated outcome will be.

The type of bond a client has with their pet will help to determine the level of diagnostics that they are willing to pursue. This will also affect their expectations of what these tests can do, and what we can do about it. Unfortunately, many clients want a guarantee of success and return to former function if they agree to the treatment options outlined by the doctor. Therefore, it is very important to not only get signed consent, but that it is informed consent. Do the clients understand what tests are being done, and have reasonable expectations as to what these tests or treatment can do for their pet?

A client that has an anthropomorphic relationship with their pet will require the most time to ensure that they understand what we can and cannot do. Many times, they will place themselves in their pet's place in deciding what tests to do and what treatments to pursue, or base this on previous personal experience. While these clients require the most time, they also want us to proceed with the utmost speed, and will typically tell us to do "whatever is necessary". If a treatment plan is not thoroughly explained there may be great discrepancies in what we view as "whatever is necessary" and what a client thinks or feels we are capable of. How many times do we hear "you can do that with animals"? Clients seldom have a good handle on what we can and will do if given free rein, or what the monetary costs will be to them, because we do expect to be compensated even if the outcome is not what the client expects. [2]

The common stereotype portrays anthropomorphically oriented owners relating to their pets as small or slow children, but these clients also tend to attribute very complex and sophisticated responses to their pets. [3] This would be the client that asks the animal if they want to have their blood drawn, and then "translates" the answer for you.

A client with a chattel relationship may indeed pursue further diagnostics or treatment options if they feel that the cost is warranted and the outcome to their liking.

The chattel orientation most commonly occurs among absentee owners; the owner of a purebred animal that is trained and handled by someone else, the shop owner who uses guard dogs for protection but has no contact with the individual animals. This can also be seen with previously anthropomorphically oriented people that have become overwhelmed emotionally with the abuse and neglect seen with some pets such as busy veterinary team members or animal welfare workers. [3] This is done as a form of protection for themselves. They obviously do not have a loving relationship with their pet and often are not able to furnish you with day to day details of their care such as food fed, toilet habits or vaccination history.

Owners that have an integrated relationship with their pet can and do have very strong relationships with their pets, but the limits that are set by these owners are usually well defined. If a situation arises that challenges these limits than we may have problems. Ours biggest problem with this type of client, is that we may not agree with the limits these clients establish. This disagreement has the potential to undermine the client-health team relationship. [3] Who among us hasn't been tempted to take over the care of a pet because they had a problem we could treat but the owners, who often have the means to treat, are unwilling to?

It is the veterinary team's job to communicate with the client before beginning the treatment and make sure that the clients understand not only any procedures involved, including any risk to the pet, the cost, but also the presumptive diagnosis the tests are being done to confirm. Most clients will not object to any procedure that they believe a legitimate purpose exists, and many will agree to those on terminally ill pets if they will provide additional information to make the pet more comfortable or experience a better quality to their life. Other clients are unwilling to perform

diagnostics if the purpose is only to diagnose what kind of cancer their pet has, if no treatment options exist or if those conflict with their beliefs. The same clients may be more than willing to do hospice care for their pet. [2]

It is in our best interests to be very upfront with clients about the diagnosis on their pets, if we candy coat the biopsy results or only tell clients the good half of the results, we do not allow them the time they need to begin to adjusting to the thought that indeed they pet may die sooner rather than later. Many times, when we are involved with a complicated case, we think only of saving the animal and give little thought to what lies ahead for that life once it is saved.[2] They owners may be physically, mentally or financially unable to cope with their pet in the aftermath of this intervention. Again, ongoing and straightforward communication is the key to keeping the situation from becoming volatile.

Many conflicts result from miscommunication. These often start out as small concerns or misunderstandings and can escalate into full blown conflicts. If left unresolved, simple misunderstandings can create hurt feelings and lead to larger problems in the future. Behind most conflicts is a client who has had their feelings hurt either because they feel that their needs were ignored, their problems or concerns were trivialized or their emotions were ridiculed.[5]

The first step is to find out when or where the miscommunication occurred, and then being willing to work things out with the client. Because this step means becoming willingly involved with an upset or hostile client, many people chose to dismiss the client's complaint and to blame them for causing turmoil. Conflict resolution is not a "winning" or losing" situation, you want to find a compromise that meets both of your needs provides a solution to the problem. Because our patients tend to have relatively short lifespan compared to our career length, taking the time to work through a conflict with a client can mean the difference between losing their business for today, and keeping it until we retire.[5]

Stages of Grief

Physician Elisabeth Kubler-Ross first described the five-stage process dying patients and their loved ones go through as they come to grips with the inevitable. [4] Many times the veterinary staff is on the receiving end of this grief, and this can precipitate many of our more dramatic crises.

These stages are:

1) Denial
2) Anger
3) Bargaining
4) Depression
5) Acceptance

The overall sequence remains essentially unchanged for most people, though variations can and do occur. We as the veterinary team go through these stages with each of our patients also. Some we progress through quite quickly and others take us some time to work through.

Denial is the most obvious stage and also one of the most difficult for us to deal with. To our very analytical minds, the results are obvious. We do not have the emotional investment many clients have in their pets, and also do not have the most to lose. Many clients move quickly from denial to anger, and this is usually directed at us; after all we found the cancer, we were unable to fix the surgical problem, we don't understand what the pet means to this owner.[4]

Clients that get stuck in the anger phase can be very trying to everyone, as much as we would like to help them, we can't do that while they're yelling at us! Recommending a second opinion may help these clients get through this phase more quickly. Many times, a client that won't hear what we're saying will accept the same information from another source more easily.[4]

Clients stuck in the bargaining phase can lure the veterinary team into treatments designed to delay the inevitable, the cost being a less-than quality life for the pet. Remember, we are primarily an advocate for the pet. Even if we can do more, is it really what should be done? The biggest tragedy with this is when the owner rationalizes that any kind of life is acceptable for the animal rather than accepting its terminal condition. [4]

Depression can be seen in many forms; sometimes it's a quiet acceptance of any treatments we recommend from a formerly vocal client or the client that is unable to make any decision regarding care for their pet. Some clients may also vacillate between depression and acceptance. Try not to push a client to make a decision at this time, a depressed person believes themselves unable to control their own lives, and those who opt for euthanasia while in this phase see the act as proof of their helplessness rather than as a caring response to a suffering pet. Instead of

helping a client through the depression, euthanasia only reinforces this depression, lengthening the time the clients will spend in the phase of their grief. [4]

Acceptance poses few problems unless the client accepts that the pet is terminal and the end is here, but the veterinary team doesn't. When clients reach acceptance, this often enables them to make any decisions regarding the dying pet's care or euthanasia with a certain calmness that team members who don't accept may see as cold and even callous.

Coping With Death

Owners coping with the death of a pet go through the same 5-step process that they went through in acceptance of its dying condition. Although denial can occur, the very nature of death makes this relatively short-lived phase. Many clients still state that they can still feel the animals' presence, but understand that they really are gone.

As with grief, the anger associated with a pet dying or being euthanized, is most often directed at the veterinary health care team. Trying to find out the cause of the anger, and working through this with the clients is in our best long-term interest. This method can only work if the client is willing to work with us, many times they will just go to another hospital without an explanation or giving us a chance. These also tend to be the clients who will bad-mouth the hospital or staff to anyone who will listen. If this behavior comes to light, do not ignore the client, as much as we'd like to. Contact them and see if you can find out the specific reason they are angry at you.

Sending a sympathy card, making a donation in their pet's name or sending flowers after their pet has died may be all that the client needs to feel that they aren't alone in their grief. While grieving for a pet is more acceptable now that it has been in the past, many people still feel a social stigma attached to openly grieving over the loss of their best friend.

Bargaining can be seen in the many varied ways that clients chose to immortalize their pets from taxidermy to mummification and cloning. These people are trying to maintain their relationship even after the death of their pet.

Depression can be seen in clients who believe that it is wrong to grieve for a pet, or have not given themselves permission to grieve. Many clients have multiple pets, and the remaining pets can help them through this phase, for those whom the deceased pet was their only friend or family, the depression can become all consuming.

Clients in the acceptance phase show the same calmness that was seen prior to the decision to euthanize or acceptance of the terminal condition. Letting client know that they excelled in caring for their pet, or sharing happy memories with them help to replace the feeling of death and dying. Other times a genuine hug is what is needed.

Client-Pet Relationship

Many times, when an animal is hospitalized, we tend to not allow clients to visit because it disrupts our work area, or causes the animal distress. If the animal is fully recovered from anesthesia, clients should be encouraged to visit. Pets are not the only ones who suffer from separation anxiety and co-dependency. An animal that is anxious and stressed with have a less than optimal response to therapy. If a twice daily visit from the owner bringing special food and blankets helps with the healing, so be it.

Trying to keep clients away from their pets can precipitate many a crisis in the ICU. Most hospitals are not equipped to have clients with their pet's full time, some clients may request this at times quite adamantly. If it does not affect the flow of the ICU or compromise the overall care of other animals, see what you can do to accommodate them. Can you set up an exam room as an ICU suite? Are the clients willing to accept the additional charges associated with this? Clients need to be made aware of the limitations of this kind of care, and what cannot be done for them. When you really think of it, this is what we tend to do with our own pets, the least we can do is allow our clients the same level of care.

Hospice is a growing trend in veterinary medicine, and something that we need to explore more often with our clients. Do you have a hospice protocol set up at your hospital? Do you have pain management techniques for terminal pets? Now is the time to do these things, not after a client requests your help.

Hospice can be as easy as explaining to the client how the end may come for their individual pet, and what they can do to make them more comfortable. Letting clients know about turning an animal over and providing appropriate bedding to prevent ulcers can help. Is their idea of clean the same as yours? Do they know about incontinence pads to absorb urine to prevent urine scald, how about using zinc oxide ointments to prevent irritation? Are pain medications being given? Just because an animal is terminal does not mean that it should be in pain. Hospice care

does not mean that all veterinary care has been terminated, the pet should still be evaluated on a regular basis and the treatment plan adjusted as necessary to preserve the quality of life the client desires.

Do not wait until the end to mention euthanasia and body disposal options to clients. This is obviously not the best time to make an informed decision. Make sure clients are aware of the euthanasia procedure for your clinic and what disposal options are available. If they desire something different, this will give them time to seek this out, rather than yelling at you because no one ever told them you didn't do taxidermy and that is what they want.

Conclusion

As with most challenges in life, communication is the key to preventing and dealing with clients in crisis situations. We need to make sure that we are all speaking the same language (literally and figuratively), that we all are working in the same direction for the pet and that we understand what our goal will be when we get there. Technicians are often an underutilized part of this puzzle. We understand what the doctor is saying and can convey this more clearly to the client. We also tend to have more time to spend with those clients that require extra time and energy. Don't let your life become a series of 15-minute appointments, spend the time and communicate with our clients, remember if they didn't care for their pets so much, we wouldn't have a job.

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Weight Loss in CKD: Is it the Protein or the Calories?

Angela Witzel Rollins, DVM, PhD, DACVN

Introduction

Weight loss is a common clinical sign associated with CKD in cats and may precede the diagnosis by up to 3 years.[1] Addressing weight loss is important as body condition is associated with survivability and longevity in cats.[2] Several factors contribute to the loss of muscle and adipose tissue with the disease including: increased energy requirements, reduced appetite, malabsorption and inflammation may all play a role.[1] There are different forms and causes of muscle loss that can be associated with this population. Sarcopenia refers to muscle loss attributed to the normal aging process. Many cats with CKD are geriatric and some degree of muscle loss is expected and likely inevitable as cats age. Cachexia is defined as cytokine-mediated degradation of muscle and adipose tissue and the metabolic derangements associated with CKD can contribute to this form of muscle wasting as well.

The restriction of protein as a dietary management strategy for CKD in cats has become increasingly controversial. Some argue cats with kidney disease should not be placed on a low protein diet in an effort to retain muscle mass and increase diet palatability while others cite research suggesting restricted protein diets, in combination with other nutrient modifications, reduce morbidity and prolong lifespan. While providing sufficient dietary protein to sustain muscle mass is an important consideration, maintaining adequate calorie intake is perhaps even more important for sustaining adequate musculature and body weight through the process of CKD.

Dietary Protein

When assessing the protein content of a diet, it is important to remember that animals actually require amino acids, rather than protein. By feeding protein sources with well-balanced ratios of essential amino acids that are readily digested and absorbed, one can lower the overall protein content of the diet while preventing protein malnutrition. It is also important to note that all diets currently marketed for management of CKD in cats exceed the recommended protein allowance set by the National Research Council. The goals behind lowering the concentration of protein in diets fed to cats with CKD are to reduce the amount of nitrogenous waste products produced during cellular metabolism, while also minimizing the amount of protein entering the glomerular filtrate of the kidneys.

Cats are obligate carnivores with higher dietary protein requirements compared to dogs. When fed inadequate amounts of protein, cats will catabolize muscle and other lean tissue to fulfill their metabolic needs, resulting in a gradual loss of lean body mass (LBM). A study evaluating varying levels of dietary protein in 20 neutered male cats over a 2 month period found cats fed 73 grams and 56 grams of protein per 1000kcal lost lean muscle mass while those fed 95 grams per 1000kcal maintained their lean mass.[3] While the results of this study are intriguing, there are a couple of limitation to consider. First, cats in the moderate protein group had lower energy intake compared to the other groups. When placed in a negative energy balance, endogenous protein is utilized for energy and this may have resulted in lower muscle mass in this group compared to the higher protein group. Second, the sample size of the study was small, with only 4 cats in the low protein group undergoing body composition analysis.

Protein restriction for managing feline CKD has been a mainstay of therapy for more than 40 years. Several studies show diets designed for CKD with restricted concentrations of phosphorus and protein increase survival in cats with IRIS stage 2 CKD and greater.[4-6] Two of the studies utilized diets that also had increased omega-3 fatty acids and lower sodium concentrations.[4,6] Based on these studies, there is strong evidence to support the use of therapeutic renal diets to reduce clinical signs of uremia and prolong survival in cats with advanced kidney disease.

Only a handful of research abstracts have evaluated lean body mass in cats with CKD. In a small study of seven cats with early CKD (creatinine ranging from 1.6-2.1 mg/dl), serum albumin and lean body mass were maintained after 30 weeks consuming a diet with 65.3 grams of protein per 1000kcal.[7] Another study of 10 cats with spontaneous CKD (staging not provided) rotated diets with 16% metabolizable energy (ME), 20% ME, and 24% ME from protein (45g, 57g, 68g of protein per 1000kcal based on 3.5 kcal/g conversion factor) for 4 month intervals.[8] The 45g protein diet resulted in lower hematocrit, weight loss despite higher calorie intake, and lower lean body mass compared to the 68 grams per 1000kcal diet. The low protein diet also resulted in lower albumin and weight loss compared to both the medium and high protein diets. These results suggest dietary protein levels close to 68 grams of protein per 1000kcal are superior to lower protein diets for cats with CKD.

A more recent study evaluated a therapeutic renal diet in cats with early stages of renal disease (IRIS Stage 1 and 2) and found no change in body weight, BUN, creatinine, urine protein:creatinine ratio (UPC), or urine specific gravity over a 12 month period.[9] Since there was no control diet in the study, it is difficult to determine if stability in renal

parameters was due to the diet, or just slow disease progression in early CKD. In addition, muscle condition was not assessed in the study, so it is difficult to determine if protein levels were adequate to sustain muscle mass.

Some information regarding the impact of protein in feline CKD can be gleaned from studies using five-sixth nephrectomy models. In one such study, cats with CKD fed a high protein diet (approximately 130 g/1000kcal) for twelve months maintained body weight while those fed a low protein (approximately 70 g/1000kcal) diet lost weight, despite similar calorie intake.[10,11] Protein intake also did not affect tubular lesion, cellular infiltrate, or fibrosis on renal histopathology. Similarly, higher protein intake did not affect GFR or UPC.[10] A similar study also using a five-sixth nephrectomy model found cats fed a high protein diet (approximately 108 g/1000kcal) had significantly lower serum creatinine, higher inulin clearance, and maintained body weight better than cats fed a diet with about 58 grams of protein per 1000kcal.[11] However, the cats on the high protein diet had higher serum urea nitrogen and developed more renal pathology. Unfortunately, there were significant limitations to this study. The higher protein diet was deficient in potassium and clinical signs of hypokalemia developed in more than one-half of the cats fed this diet.

Calorie Intake

Reduced appetite is a common clinical finding in cats with CKD. Factors such as dehydration, electrolyte imbalances, acidemia, uremia, oral ulcerations, gastritis, and anemia can contribute to reduced food intake.[12] Cats have a median weight loss of approximately 10% of their body weight in the 12 months prior to diagnosis of CKD.[1,13] The rate of weight loss also increases after diagnosis.[1] Lower body weights are associated with shorter survival times in both dogs and cats with CKD.[1,14]

Studies assessing calorie intake in cats with CKD are sparse. One study fed 20 adult cats with IRIS stage 1 and 2 CKD one of two therapeutic renal diets with similar protein contents (67g/1000kcal) for 6 months.[15] Cats in one diet group consumed an average of 23% fewer calories. This group also showed significant weight loss (13% of body weight) and loss of lean tissue (11%). Notably, the cats in the group consuming adequate calories (mean 207 kcal/day) maintained lean muscle and body weight on protein levels typical of therapeutic renal diets.[15] This study suggests calorie intake plays a larger role in maintaining lean mass in cats with CKD than total protein content. However, it is critical that amino acid profiles be optimal when feeding lower concentrations of total dietary protein in cats.

Management of Hyporexia

The metabolic derangements associated with CKD can reduce appetite. It is important to provide an optimal feeding environment when introducing and transitioning cats to a therapeutic renal diet. New diets should be introduced very slowly when the cat is comfortable and ideally in the home environment. Owners may start with ¼ new food with ¾ old food for 5-7 days and gradually change the proportions over several weeks if needed. A new feeding system will soon be available in the United States that allows cat owners to track their cat's food intake through a phone app, which may be a valuable tool for preventing weight loss.[a] Other tips to improve the feeding environment include:

- Feed in a calm, quiet place with minimal interference from other pets or children.
- Use wide, shallow bowls or plates to avoid whiskers bending.
- Provide a variety textures. Try canned foods with shredded, minced, chunk, or pate textures or dry kibble to determine preference.
- Increase freshness and aroma by heating canned foods.

Management of Weight Loss

Medical therapy can also be used to manage weight loss. Historically compounded transdermal and human generic oral versions of mirtazapine have been used in veterinary medicine. An FDA-approved transdermal mirtazapine preparation Mirataz® (mirtazapine transdermal ointment) indicated for the management of weight loss in cats is commercially available and provides better dosage consistency compared to compounded preparations.[b] A large multi-center, double-blind, placebo-controlled, randomized clinical trial study in cats with >5% unintended weight loss demonstrated that 2 mg of Mirataz applied to the inner ear pinnae for 14 days resulted in significantly more weight gain compared to placebo (3.94% ± 5.37% versus 0.41% ± 3.33%).[16] While this modest improvement in body weight is helpful, other measures such as esophagostomy feeding tube (E-tube) placement may also be necessary. E-tubes can be used long-term and provide appropriate nutrition, help maintain hydration, and are a convenient route for medication administration. While owners are often initially resistant to the idea of feeding tubes, it is important to emphasize that cats can freely eat with E-tubes in place and the tubes are well-tolerated by most cats. Overall, E-tubes can relieve owner stress about medication administration, subcutaneous fluid injections, and proper nutrient

[a] Microchip Pet Feeder Connect. SureFlap Ltd. Clearwater FL, US
[b] Mirataz.® Kindred Biosciences, Inc. Burlingame, CA, US.

intake and should be considered in cats that begin to lose weight secondary to CKD. A comprehensive review of E-tube use in cats with CKD is available.[12]

Important Safety Information

Mirataz® (mirtazapine transdermal ointment) is for topical use in cats only under veterinary supervision. Do not use in cats with a known hypersensitivity to mirtazapine or any of the excipients. Do not use in cats treated with monoamine oxidase inhibitors (MAOIs). Not for human use. Keep out of reach of children. Wear gloves when handling/applying, wash hands after and avoid contact between the treated cat and people or other animals for 2 hours following application. Use with caution in cats with hepatic and kidney disease. Cat's food intake should be monitored upon discontinuation. Safety has not been evaluated in cats less than 2 kg, less than six months of age or in breeding, pregnant or lactating cats. The most common adverse reactions observed during clinical trials were application site reactions, behavioral abnormalities (vocalization and hyperactivity) and vomiting.
For complete prescribing information see www.kindredbio.com/mirataz-pi.

Conclusions

More research is needed to determine the optimal protein and amino acid profiles for cats with various stages of CKD. When calorie intake is sufficient and high-quality protein sources are used, cats with early CKD maintain muscle mass on the moderately low protein concentrations typical of most therapeutic renal diets. However, cats with IRIS stage 1 and early stage 2 CKD can likely tolerate and may benefit from higher protein concentrations. It is important to remember that therapeutic renal diets have many factors beyond protein restriction that benefit CKD. Reduced phosphorus and high concentrations of the omega 3 fatty acids EPA and DHA are also critical components. Therapeutic diets are now available for cats with early stages of CKD that provide higher protein concentrations while also balancing other nutrient concerns of CKD.[cd]

Maintaining adequate calorie intake may play an even more important role in maintaining body composition than dietary protein intake. New tools will soon be available to track food intake. The FDA-approved medication to manage weight loss is used in cats with CKD; however, long-term safety has not been evaluated and warrants more research. Clinicians should also become more comfortable recommending feeding tubes for long-term food and medication administration.

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[c] NF Kidney Function® Early Care Feline Formula, Nestlé Purina Pet Care, St. Louis MO, US.
[d] Hill's® Prescription Diet® k/d® Early Support Feline Chicken Dry Food, Hills Pet Nutrition, Topeka KS, US.

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Mirataz™
(mirtazapine transdermal ointment)

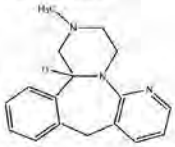
Each 1 g of Mirataz™ contains 20 mg mirtazapine (2%). Each 5 g tube contains 100 mg (0.1 g) of mirtazapine.

For topical application in cats only. Not for oral or ophthalmic use.

CAUTION:
Federal law (USA) restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Mirataz™ (mirtazapine transdermal ointment) is a white to off-white ointment containing 2% (w/w) of mirtazapine suitable for transdermal (topical) administration. Mirataz™ contains the following inactive ingredients: Polyethylene Glycol (PEG) 400, PEG 3350, Diethylene Glycol Monoethyl Ether, PEG-8 Caprylic/Capric Glycerides, Oleyl Alcohol, Butylated Hydroxytoluene, Dimethicone, and Dry Flo TS.

The structural formula of mirtazapine is:



Molecular Formula: $C_{17}H_{19}N_3$ Molecular Weight: 265.35

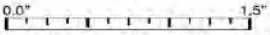
INDICATION:
Mirataz™ is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION:
Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days (see Diagrams below).

Wear disposable gloves when applying Mirataz™. Dispose of used gloves after each application.

Alternate the daily application of Mirataz™ between the left and right inner pinna of the ears. Do not administer into the external ear canal. If desired, the inner pinna of the cat's ear may be cleaned by wiping with a dry tissue or cloth immediately prior to the next scheduled dose. If a dose is missed, apply Mirataz™ the following day and resume daily dosing.

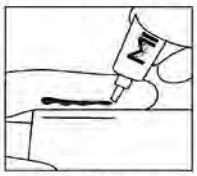
To demonstrate the method of administering the dose, the veterinarian or trained personnel at the clinic should apply the first dose in the presence of the owner.



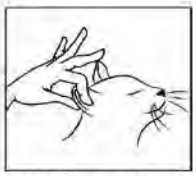
This ruler measures 1.5 inches. Use this ruler to measure the 1.5 inch ribbon of ointment to be applied.

To apply Mirataz™:

Step 1: Wear disposable gloves. Twist cap on tube counterclockwise to open.



Step 2: Apply even pressure on tube and squeeze a 1.5-inch line of ointment onto your gloved finger using the measured line on the carton or in this package insert.



Step 3: Using your gloved finger, gently rub ribbon of ointment on inside pinna of the cat's ear spreading it evenly over the surface. Dispose of used gloves after each application. If contact with your skin occurs wash thoroughly with soap and warm water.

CONTRAINDICATIONS:
Mirataz™ is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients.

Mirataz™ should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) (e.g. selegiline hydrochloride (L-deprenyl), amitraz), as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS:
Not for human use. Keep out of reach of children.

Wear disposable gloves when handling or applying Mirataz™ to prevent accidental topical exposure. After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing.

In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention.

In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

PRECAUTIONS:
Do not administer orally or to the eye.

Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See Animal Safety).

Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure.

Upon discontinuation of Mirataz™, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat.

Mirataz™ has not been evaluated in cats < 2 kg or less than 6 months of age. The safe use of Mirataz™ has not been evaluated in cats that are intended for for breeding, pregnant, or lactating cats.

ADVERSE REACTIONS:
In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Mirataz™ and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Mirataz™ without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. The adverse reactions observed in the study and number of cats experiencing each adverse reaction is summarized in Table 1 below.

Table 1. Adverse Reactions Reported During the Field Study

Adverse Reaction	Mirataz™ N=115 (%)	Vehicle Control N=115 (%)
Application site (Ear pinna)		
Erythema	12 (10.4%)	20 (17.4%)
Crust/Scab	3 (2.6%)	6 (5.2%)
Residue	3 (2.6%)	8 (7.0%)
Scaling/Dryness	3 (2.6%)	3 (2.6%)
Dermatitis or irritation	1 (0.9%)	9 (7.8%)
Alopecia	1 (0.9%)	2 (1.7%)
Pruritus	1 (0.9%)	4 (3.5%)
Behavioral		
Vocalization	13 (11.3%)	2 (1.7%)
Hyperactivity	8 (7.0%)	1 (0.9%)
Disoriented state or ataxia	4 (3.5%)	2 (1.7%)
Lethargy/weakness	4 (3.5%)	9 (7.8%)
Attention Seeking	3 (2.6%)	0
Aggression	2 (1.7%)	0
Physical Examination or Observational		
Vomiting	13 (11.3%)	15 (13.0%)
Dehydration	6 (5.2%)	5 (4.3%)
Diarrhea or soft stool	6 (5.2%)	7 (6.1%)
Heart murmur	5 (4.3%)	7 (6.1%)
Inappetence	5 (4.3%)	5 (4.3%)
Renal insufficiency*	4 (3.5%)	0
Ear infection	3 (2.6%)	0
Urinary tract infection	3 (2.6%)	0
Clinical Pathology		
Hematuria	7 (6.1%)	1 (0.9%)
Elevated BUN (without creatinine)**	6 (5.3%)	0
Elevated creatinine and BUN	5 (4.3%)	1 (0.9%)
Hyperphosphatemia	5 (4.3%)	0
Hypokalemia	5 (4.3%)	2 (1.7%)
Pyuria	5 (4.3%)	0
Anemia	3 (2.6%)	8 (7.0%)
Low urine specific gravity	3 (2.6%)	1 (0.9%)
Monocytosis	3 (2.6%)	2 (1.7%)
Neutrophilia	3 (2.6%)	2 (1.7%)

* One cat with renal insufficiency was reported with a serious adverse reaction of acute renal failure, hematuria, and pyuria at the Week 2 visit. The cat was enrolled with a history of chronic kidney disease. Euthanasia was elected and necropsy revealed hypertrophic cardiomyopathy, bilateral parathyroid hyperplasia, and mild to moderate renal disease.
** At Week 2, blood urea nitrogen (BUN) values were significantly higher in the Mirataz™ group compared to the vehicle control group ($p<0.10$). The BUN in the Mirataz™ group was 43.60 mg/dL (reference range 16-37 mg/dL) compared to 36.05 mg/dL in the vehicle control group.

Post study, follow-up was done in 199 cats (103 in the Mirataz™ (mirtazapine transdermal ointment) group and 96 in the vehicle control group). Following cessation of Mirataz™, four cats were reported as being less social or less restless, one cat was reported as more active, and one cat was reported with increased hissing and urinating out of the litter box.

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Kindred Biosciences, Inc. at 888-608-2542.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at
http://www.fda.gov/AnimalVeterinary/SafetyHealth

INFORMATION FOR CAT OWNERS:
Upon discontinuation of Mirataz™, it is important to monitor your cat's food intake. Your cat's food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days or if your cat stops eating for more than 48 hours, contact your veterinarian.

CLINICAL PHARMACOLOGY:
Mechanism of Action:
The exact mechanism by which mirtazapine induces weight gain has not been clearly elucidated but appears to be multifactorial.[1] Mirtazapine is an α2-adrenergic receptor antagonist nor-adrenergic and serotonergic antidepressant drug. Mirtazapine is known to be a potent antagonist of 5-HT2 and 5-HT3 serotonin receptors in the central nervous system (CNS), and a potent inhibitor of histamine H1 receptors. Because mirtazapine blocks 5-HT2 and 5-HT3 receptors, only 5-HT1A-mediated serotonergic transmission is enhanced. Inhibition of 5-HT2 receptors may account for the orexigenic effects of mirtazapine. Another hypothesis is that mirtazapine induced weight gain may be secondary to changes in leptin and the tumor necrosis factor (TNF-α) cytokine system.[2] A study by Fernstrom (1995) demonstrated a reduction of the basal metabolic rate in patients treated with antidepressants in general.[3]

Pharmacokinetics:
In a crossover study in eight cats to determine the relative bioavailability of oral and transdermal 2% mirtazapine, the mean half-life (26.8 hours) with topical administration was over 2X longer than the mean half-life (10.1 hours) with oral administration.

The doses used in the target animal safety study were higher (2.8 to 5.4 mg) than the label dose. Based on dose proportionality in $AUC_{0-\infty}$ and C_{max} observed in this study, these pharmacokinetic parameters were extrapolated for the 2 mg/cat label dose administered once per day for 35 days (see Table 2).

Steady state was achieved within 14 days. The median accumulation between first and 35th dose was 2.71X (based on AUCratio) and 3.90X (based on C_{max} ratio).

Table 2. Plasma pharmacokinetic parameters at steady state after 2 mg/cat dose of mirtazapine 2.0% transdermal ointment in healthy cats

Parameter	Unit	Mean (SD)
C_{max}	ng/mL	32.1 (19.9)
T_{max}	hr	6 (2.6)[a]
$AUC_{0-\infty}$	hr*ng/mL	410.3 (213.5)
Half-life[b]	hr	11.2 (2.98)

C_{max} = extrapolated maximum plasma concentration
[a]T_{max} = time to maximum plasma concentration (reported as median and range)
$AUC_{0-\infty}$ = extrapolated area under the plasma time vs. concentration curve
[b]The half-life value is reflective of both topical and oral exposure. In another study where cats wore Elizabethan collar to restrict access to their ears and consequent oral exposure, a longer half-life (Mean= 20.7 hr) was observed.

EFFECTIVENESS:
The effectiveness of Mirataz™ (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds.

Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Mirataz™ to vehicle control. A total of 230 cats were enrolled and received either Mirataz™ (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear.

A total of 177 cats were determined to be eligible for the effectiveness analysis: 83 cats were in the Mirataz™ group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit.

At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant (p<0.0001) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Mirataz™ group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

ANIMAL SAFETY:
The margin of safety of mirtazapine was evaluated in one laboratory study, a comprehensive review of six pilot studies (five laboratory and one clinical) utilizing the final market formulation, and one laboratory study that was not final market formulation.

Laboratory Safety Study:
In a 6-week laboratory safety study, 48 healthy cats aged 7-10 months were dosed topically with mirtazapine once daily at 0 mg/kg (vehicle control), 1.1 mg/kg (1.4 to 2.7X), 3.2 mg/kg (4.3-7.5X), and 5.3 mg/kg (7.1-12.2X) body weight. Four cats/sex/group in the 1.1 and 3.2 mg/kg groups were dosed topically to the inner pinna of the ear, alternating between right and left ears. Eight cats/sex/group in the 0 and 5.3 mg/kg groups were dosed topically to the inner pinna of the ear, splitting the dose between both ears. Four cats/sex/group in the 0 and 5.3 mg/kg groups were maintained and monitored during a 4-week recovery period.

6 Week Dosing Period
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Mirtazapine administration resulted in increased vocalization, hyperactivity, attention-seeking behaviors, and tremors in all mirtazapine dose groups. Frank blood in the stool was infrequently observed in the vehicle control, 3.2, and 5.3 mg/kg groups. Polyuria was observed in all groups. Polydipsia was observed in one cat in the 5.3 mg/kg group. These cats (one from each mirtazapine-dose group) were isosthenuric. Eight cats developed cystitis with or without urethral obstruction throughout the study in all groups. One cat each from the vehicle control and 3.2 mg/kg group were euthanized early on Day 35 due to urethral obstruction.

Two cats from the 1.1 mg/kg group had either ventricular premature contractions (VPC) or tall R waves, and one cat from the 5.3 mg/kg group had both VPC and a right axis deviation.

Eosinophilia was noted sporadically in the vehicle control, 1.1, and 5.3 mg/kg groups. Mild elevations in ALT values were noted sporadically in vehicle control, 3.2, and 5.3 mg/kg groups. On Day 15, one cat in the 3.2 mg/kg group demonstrated a marked ALT elevation of 3397 U/L, with concurrent elevations in AST and GGT. By Day 42, the ALT declined to 109 U/L and the AST and GGT returned to within normal limits.

Gross pathology findings, confirmed with histopathology, were hyperplastic dermatitis (alopecia, hyperkeratosis, thickening, and ceruminous gland secretion) of the pinnae in all cats and findings consistent with cystitis (mucosal urinary bladder hemorrhage, mottled dark red appearance, and irregular contour) in four male cats (two vehicle control, one 3.2 mg/kg and one 5.3 mg/kg). Additional histopathologic findings included pyelonephritis (two vehicle control and one 5.3 mg/kg), nephrocalcinosis (three vehicle control, one 1.1 mg/kg, three 3.2 mg/kg, and one 5.3 mg/kg), necrosis of the kidneys (one vehicle control and one 3.2 mg/kg), unilateral hypoplasia of the thyroid gland (two 5.3 mg/kg), and unilateral hypertrophy of the thyroid gland (one 5.3 mg/kg).

4 Week Recovery Period
Following a 4-week recovery period, ALT elevations resolved. Polyuria was reduced and only occurred in two cats in the 5.3 mg/kg group. Pinnal lesions (erythema and flaking) completely resolved in the vehicle control and improved in the 5.3 mg/kg groups. Ear thickening improved in both groups.

Pilot Safety Studies:
In six pilot studies (five laboratory and one clinical study) utilizing the final market formulation of Mirataz™, and one laboratory study that utilized non-final market formulation, a total of 76 cats were administered mirtazapine. Five studies administered mirtazapine ointment topically (0.5-5.3 mg/kg), one study administered mirtazapine topically and orally (0.5 mg/kg), and one study administered mirtazapine orally (10.6 mg/cat).

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One study reported six cats with blood in the stool. Two studies reported one cat each showing aggression. One study reported polyuria in one cat, another study reported stranguria and possible urinary tract infection in one cat. Two studies reported cardiac abnormalities, including sinus tachycardia not present at baseline, development of a grade 3/6 heart murmur, tall QRS complexes and left or right axis deviation. One study reported one cat with ataxia. In the studies that administered mirtazapine orally, salivation and lip licking were frequently observed.

In the terminal study administering 5.3 mg/kg mirtazapine topically, histopathology showed chronic hyperplastic dermatitis at the application site.

STORAGE:
Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.

HOW SUPPLIED:
Mirataz™ is supplied in a 5 gram aluminum tube.

REFERENCES

1. Carmel, M., Kramer-Reinstadler, K., Rauchenzauner, M., Lechner-Schoner, T., Strauss, R., Engl, J., & Ebenbichler, C. F. (2006). Effect of mirtazapine treatment on body composition and metabolism. The Journal of clinical psychiatry, 67(3), 421-424.
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Post study, follow-up was done in 199 cats (103 in the Mirataz™ (mirtazapine transdermal ointment) group and 96 in the vehicle control group). Following cessation of Mirataz™, four cats were reported as being less social or less restless, one cat was reported as more active, and one cat was reported with increased hissing and urinating out of the litter box.

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Kindred Biosciences, Inc. at 888-608-2542.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at
http://www.fda.gov/AnimalVeterinary/SafetyHealth

INFORMATION FOR CAT OWNERS:
Upon discontinuation of Mirataz™, it is important to monitor your cat's food intake. Your cat's food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days or if your cat stops eating for more than 48 hours, contact your veterinarian.

CLINICAL PHARMACOLOGY:
Mechanism of Action:
The exact mechanism by which mirtazapine induces weight gain has not been clearly elucidated but appears to be multifactorial.[1] Mirtazapine is an α2-adrenergic receptor antagonist nor-adrenergic and serotonergic antidepressant drug. Mirtazapine is known to be a potent antagonist of 5-HT2 and 5-HT3 serotonin receptors in the central nervous system (CNS), and a potent inhibitor of histamine H1 receptors. Because mirtazapine blocks 5-HT2 and 5-HT3 receptors, only 5-HT1A-mediated serotonergic transmission is enhanced. Inhibition of 5-HT2 receptors may account for the orexigenic effects of mirtazapine. Another hypothesis is that mirtazapine induced weight gain may be secondary to changes in leptin and the tumor necrosis factor α(TNF-α) cytokine system.[2] A study by Fernstorm (1995) demonstrated a reduction of the basal metabolic rate in patients treated with antidepressants in general.[3]

Pharmacokinetics:
In a crossover study in eight cats to determine the relative bioavailability of oral and transdermal 2% mirtazapine, the mean half-life (26.8 hours) with topical administration was over 2X longer than the mean half-life (10.1 hours) with oral administration.

The doses used in the target animal safety study were higher (2.8 to 5.4 mg) than the label dose. Based on dose proportionality in $AUC_{0\text{-}24hr}$ and C_{max} observed in this study, these pharmacokinetic parameters were extrapolated for the 2 mg/cat label dose administered once per day for 35 days (see Table 2).

Steady state was achieved within 14 days. The median accumulation between first and 35th dose was 3.71X (based on AUC ratio) and 3.90X (based on C_{max} ratio).

Table 2. Plasma pharmacokinetic parameters at steady state after 2 mg/cat dose of mirtazapine 2.0% transdermal ointment in healthy cats

Parameter	Unit	Mean (SD)
C_{max}	ng/mL	32.1 (19.9)
T_{max}	hr	6 (2-6)[a]
$AUC_{0\text{-}24hr}$	hr*ng/mL	410.3 (213.5)
Half-life[b]	hr	11.2 (2.98)

C_{max} = extrapolated maximum plasma concentration
[a]T_{max} = time to maximum plasma concentration (reported as median and range)
$AUC_{0\text{-}24hr}$ = extrapolated area under the plasma time vs. concentration curve
[b]The half-life value is reflective of both topical and oral exposure. In another study where cats wore Elizabethan collar to restrict access to their ears and consequent oral exposure, a longer half-life (Mean= 20.7 hr) was observed

EFFECTIVENESS:
The effectiveness of Mirataz™ (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds.

Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Mirataz™ to vehicle control. A total of 230 cats were enrolled and received either Mirataz™ (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear.

A total of 177 cats were determined to be eligible for the effectiveness analysis: 83 cats were in the Mirataz™ group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit.

At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant ($p<0.0001$) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Mirataz™ group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

ANIMAL SAFETY:
The margin of safety of mirtazapine was evaluated in one laboratory study, a comprehensive review of six pilot studies (five laboratory and one clinical) utilizing the final market formulation, and one laboratory study that was not final market formulation.

Laboratory Safety Study:
In a 6-week laboratory safety study, 48 healthy cats aged 7-10 months were dosed topically with mirtazapine once daily at 0 mg/kg (vehicle control), 1.1 mg/kg (1.4 to 2.7X), 3.2 mg/kg (4.3-7.5X), and 5.3 mg/kg (7.1-12.2X) body weight. Four cats/sex/group in the 1.1 and 3.2 mg/kg groups were dosed topically to the inner pinna of the ear, alternating between right and left ears. Eight cats/sex/group in the 0 and 5.3 mg/kg groups were dosed topically to the inner pinna of the ear, splitting the dose between both ears. Four cats/sex/group in the 0 and 5.3 mg/kg groups were maintained and monitored during a 4-week recovery period.

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REFERENCES:
1. Laimer, M., Kramer-Reinstadler, K., Rauchenzauner, M., Lechner-Schoner, T., Strauss, R., Engl, J., & Ebenbichler, C. F. (2006). Effect of mirtazapine treatment on body composition and metabolism. The Journal of clinical psychiatry, 67(3), 421-424.
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It's so HARD! Feline Heartworm Case Management & Diagnostic Updates

Byron Blagburn, MS, PhD

Background

Heartworm infection in dogs was first described in 1626. However, feline heartworm infections were not documented in the United States until 1922.[1] Although canine and feline infections are caused by *Dirofilaria immitis*, there are differences in infections in the two hosts (Table 1). The prevalence of feline heartworm infection continues to increase, likely including more than 16 countries and well over 30 US states.[2] Because of increased awareness and improved diagnostic methods, feline heartworm infection is diagnosed with increasing frequency in veterinary hospitals.[3] Interestingly, given the potential for heartworms to cause severe disease or death in cats, some have estimated that less than 5% of cats in the United States receive a heartworm preventive medication.[4]

Heartworm Associated Respiratory Disease (HARD)

Initially, feline heartworm disease was thought to be due to the presence and subsequent death of mature heartworms in the heart or lungs of cats.[2] Clinical signs were caused by death of these worms leading to compromised lung function and signs such as coughing, dyspnea and wheezing. Additional signs may include salivation, vomiting, diarrhea and hemoptysis. Continuing research suggests that early death of immature heartworms in cats can also evoke severe and potentially fatal pulmonary reactions.[3] Moreover, these infections cannot be easily diagnosed using antigen tests, antibody tests, or radiography because of the absence of adult female heartworms, potentially waning antibody levels, and/or the similarity of lung lesions to those associated with other feline pulmonary diseases.

In cats, immature worms arrive in the lungs 70-90 days after infection. However, because of the cat's unique pulmonary response, most of these worms are killed in the lungs and do not survive to the adult stage. The intense inflammation caused by the death of these immature adult heartworms results in respiratory disease characterized by coughing and dyspnea. Because these signs correspond to the death of these worms about 90 days after infection, disease was attributed to 3-month-old worms, and was referred to as the 3-month disease cycle.[3] In a laboratory model of feline heartworm disease, we reproduced the 3-month-disease cycle by strategically treating experimentally infected cats to eliminate 70-90 day-old heartworms. Results demonstrated that experimentally-induced death of immature heartworms in the lungs can cause clinical disease identical to the naturally occurring 3 month disease. This syndrome was named heartworm associated respiratory disease and given the acronym HARD to characterize the potential for cats to present with heartworm disease that is not caused by mature heartworms (Figures 1a and 1b).[5-7] Radiographs of the lungs of cats with abbreviated infections (HARD) were similar to radiographs of cats with naturally occurring heartworm (Figures 2a and 2b), and other pulmonary diseases such as feline asthma. In support of naturally occurring HARD, Browne et al[8] demonstrated a correlation between antigen, antibody, and necropsy results that were similar to those of our HARD study. They also correlated these test results with lung lesions, concluding that cats can have lesions consistent with heartworm infection, but without serologic or necropsy confirmation of heartworm infection.[8]

Our HARD studies, taken with the Browne et al study should alert veterinarians that heartworm disease in cats can be caused by immature heartworms and that diagnosis of these infections can be challenging. It is important to note that specific therapies for HARD are unknown at this time. Cats with HARD can only be treated symptomatically as described below. A comparison of HARD and feline heartworm disease caused by mature heartworms worm is presented in table 2.

Diagnosis of HARD and feline heartworm infection

Heartworm disease in cats is difficult to diagnose and is often mistaken for other diseases. Heartworm infected cats often are asymptomatic or present with a history of transient clinical signs. An array of tests can be employed when either HARD or heartworm disease caused by mature worms is suspected (Table 2). Serologic tests are available as both point-of-care and reference laboratory tests for detection of antigen or antibodies specific for *D. immitis*. A positive antigen test or a positive echocardiogram is diagnostic for heartworm in cats infected with mature worms. These tests are not helpful for confirming or ruling out HARD. Radiography may be helpful, although lesions are not specific for heartworm disease. Antibody tests are useful in confirming that infective larvae were introduced by mosquitoes and that sufficient development occurred to induce an antibody response. When used with presenting clinical signs, a positive antibody test raises the index of suspicion for heartworm. Other laboratory tests such as a CBC and chemistry panel can provide marginally helpful ancillary data, but include no definitive test parameter that is diagnostic for heartworm. Necropsy examination is definitive of course but cannot be applied under ante-mortem

circumstances. Necropsy examination is also useful in confirming that heartworms are the cause of lesions and/or disease due to aberrant heartworm migration.

Recently, a phenomenon referred to as “antigen-blocking” has complicated our interpretation of a negative antigen tests in both dogs and cats.[10,11] Under conditions of antibody excess, antibodies may bind to circulating heartworm antigen and prevent the capture of antigen by substrate-bound capture antibodies. This blocking phenomenon can be reversed by either heat or acid treatment of serum or plasma. These reversal procedures dissociate heartworm antigen and antibody complexes to then allow the antigen to be captured by the substrate-bound antibody and confirm the presence of heartworm antigen.

Because of the lack of specificity of clinical signs, it is likely that a combination of the tests and diagnostic methods mentioned above will be necessary to confirm heartworm disease in cats (Table 2). As with other diseases, a detailed history including travel, current geographic location and indoor/outdoor habits can be helpful in interpreting clinical signs and test results.

Treatment of HARD and feline heartworm infection

Treatment of mature heartworm infections and HARD is palliative at best. Strategies are to reduce clinical signs until either heartworms are eliminated by natural host mechanisms or a normal balance of the host-parasite relationship is re-established. Information on the use of melarsomine dihydrochloride to eliminate adult worms in cats is inadequate and inconsistent. Efficacy against transplanted worms using both standard 2-dose regimen and the alternative 3-dose regimen yielded reductions in worm burdens without severe adverse events, but assuming these results will be achieved under the spectrum of conditions that occurs in naturally infected cats is presumptive and potentially dangerous. Use of melarsomine in naturally infected cats often resulted in host mortality or unacceptable adverse events.[2] Current thought leaders do not recommend the use of heartworm adulticides in cats.

Surgical removal of heartworms from accessible locations remains a viable alternative, assuming the person performing the procedure possesses the necessary surgical skills. The advantage to surgery is that it eliminates the likely thromboembolic events that results from chemotherapeutic removal of heartworms from cats. As mentioned, palliative therapy including oxygen, corticosteroids, bronchodilators and anti-platelet drugs (other than aspirin) have been helpful in managing clinical signs associated with HARD and adult worm death and thromboembolism.[2] Even with adequate supportive therapy, 10% to 20% of cats with symptomatic heartworm infections will likely die from respiratory complications.[9]

Many cats with HARD and thromboembolic disease will survive. However, the risk of death or disease complications is not acceptable given the availability of safe and effective preventive products. Products are available with single actives (ivermectin, milbemycin oxime, selamectin) and as combinations (moxidectin/imidacloprid, selamectin/sarolaner, and eprinomectin/praziquantel). The spectrum of many of the products also includes gastrointestinal parasites, fleas and mites. Newer combinations also carry label indication for ticks. Future products will likely extend the label claims for heartworms and others parasites beyond 1 month. This is important because it will encourage pet owners to embrace feline heartworm prevention and improve compliance.

TABLE 1
Comparison of Canine and Feline Heartworm Infections

Dogs	***Cats***
Often harbor many heartworms	Usually harbor few heartworms
Likely to be antigen positive because of the presence of female worms	Less likely to be antigen positive because of few worms, thus few female worms
Microfilariae are often present	Microfilariae are seldom present
Antibodies are not helpful in the diagnosis	Antibodies may be helpful in the diagnosis
The heart and lungs are involved in disease	The heart is not usually involved in disease; the lungs can be severely affected

Disease depends on the size of the dog, number of worms, and the dog's activity level	Disease can be caused by a single heartworm
HARD is not described in dogs	HARD is suspected in an unknown number of feline heartworm cases

Table 2. Comparison of Heartworm-Associated Respiratory Disease (HARD) and disease produced by mature heartworms in cats. From reference 2 with modifications

Heartworm Factor	HARD (Heartworm- Associated Respiratory Disease)	Heartworm Disease Caused by Mature Worms
Onset of clinical signs after infection	Approximately 3 months	7 months or more
Cause	Death of immature heartworms in the pulmonary arteries	Presence, death and disintegration of adult heartworms in the pulmonary arteries
Clinical Disease	Dyspnea, coughing, wheezing	Dyspnea, coughing, hemoptysis, collapse, vomiting, sudden death
Diagnostic test results		
Serology/Microfilariae		
Antibody	Often positive	Often positive
Antigen	Negative	Positive or Negative
Microfilariae	Negative	Rarely positive
Radiography	Broncho-interstitial lesions	Variable broncho-interstitial lesions, pulmonary artery enlargement, pulmonary hyperinflation, rarely pleural effusion and consolidation
Echocardiography	Normal (no heartworms present)	Heartworms may be present in the pulmonary artery, right atrium or right ventricle

Figure 1a. Lungs from an experimentally infected cat receiving heartworm prevention.

Figure 1b. Lungs from a cat with experimentally induced heartworm-associated respiratory disease (HARD).

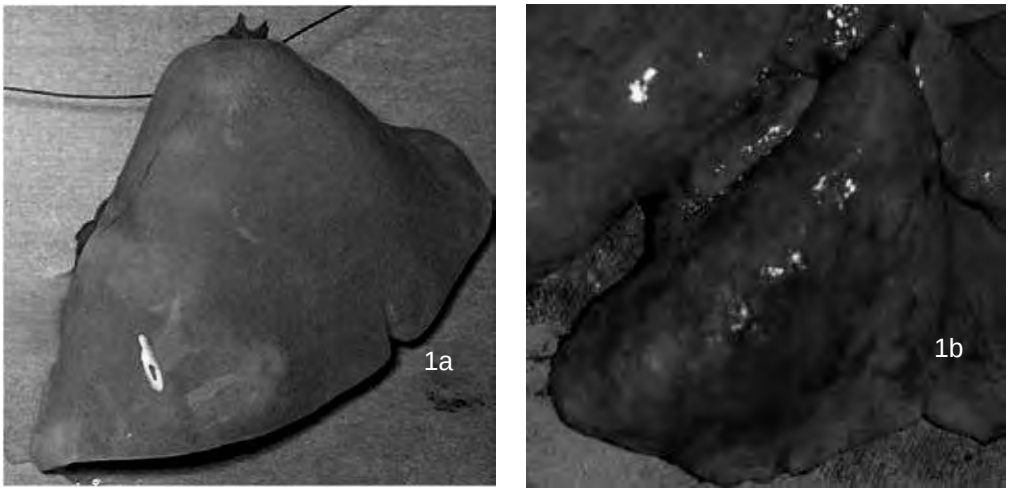
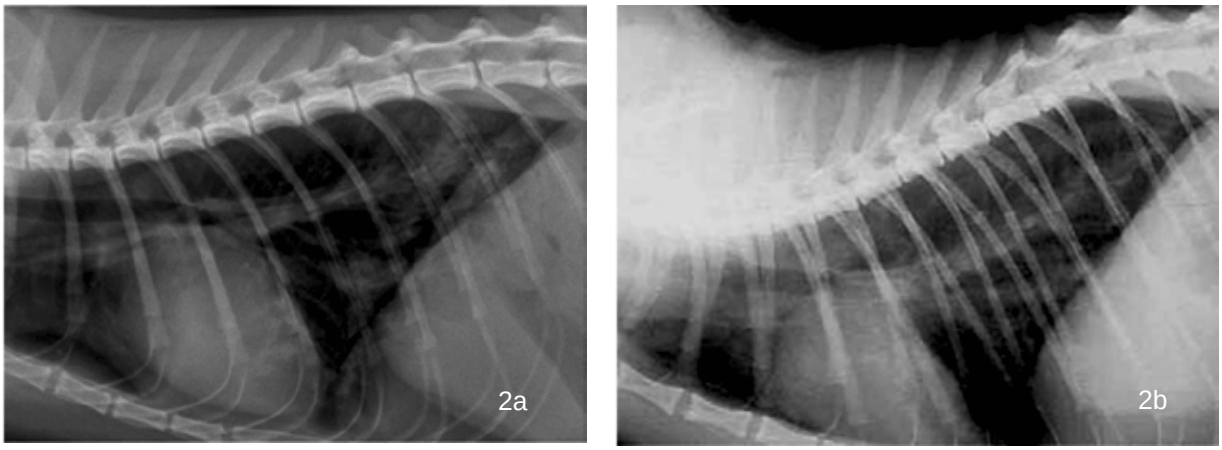


Figure 2a. Radiograph of cat with heartworm-associated respiratory disease (HARD).

Figure 2b. Radiograph of cat with naturally occurring heartworm disease and caval syndrome. Note the similarities between HARD and naturally occurring disease. (Source: Venco *et al*., *Veterinary Parasitology* 158 (2008) 232-237).



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NOTES:

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Controlled Substances 101: How & Why You Must Comply!

Jan Woods

The purpose of this presentation is to increase controlled substance regulatory compliance awareness, meet continuing education opioid (CEs) requirements, reduce risk and discuss increased savings through improved record keeping and inventory controls.

Brief Overview of Presentation

1. Learn how to minimize your risk by instituting effective controlled substance systems. Presented by a previous veterinary practice co-owner, hospital administrator, management consultant and public speaker/educator, who has worked with DVM's cited by the DEA!
2. Learn what's really required by the DEA for controlled substance compliance in your practice.
3. Learn how the DEA's controlled substance regulations affect your practice every day.
4. Learn why you should follow the DEA's controlled substance regulations, when you feel that nobody else does.
5. Learn more about the recent opioid shortage and how it affects your practice.
6. Learn how to effectively and efficiently manage your controlled substances, according to regulations and best practice suggestions.
7. Learn how to make your controlled substance inventories easier and more accurate.
8. Learn what to do if your practice experiences an internal or external loss or theft of controlled substances.
9. Learn what to do if a DEA Agent/Auditor, or any other State or Federal agent comes to inspect your practice.
10. Learn how to think like an auditor.
11. Learn how to minimize your risk.

References

1. The Controlled Substances Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970
2. DEA clarifies reporting of controlled substance loss. Federal Register: July 8, 2003 (Volume 68, Number 130)][Proposed Rules] [Page 40576-40579] From the Federal Register Online via GPO Access [wais.access.gpo.gov][DOCID:fr08jy03-20] DEPARTMENT OF JUSTICE Drug Enforcement Administration21 CFR Part 1301[Docket No. DEA-196P]RIN 1117-AA73
3. FEDERAL Recordkeeping Requirements
4. Code of Federal Regulations, Section 1304.11 Inventory Requirements
5. Practitioner's Manual, can be found on the internet at DEA's Web Site (under "publications" www.DEAdiversion.usdoj.gov

Note: The government changes laws frequently. As of August 2019, the information presented in Controlled Substances 101: How & Why You Must Comply! is current. Remember to check frequently with various governmental agencies and/or your attorney for changes that may affect your hospital/clinic.

Please feel free to call my cell at 913-302-4999 or email me at jwoods@cubex.com with any questions that you many have.

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Complex Disease Management

Exploring Feline Comorbidities

Oct. 31 – Nov. 3, 2019
Hilton San Francisco
Union Square
San Francisco, CA

SUNDAY, NOVEMBER 3, 2019

TIME	SESSION TITLE	SPEAKER	ROOM	SPONSOR/ PARTNER
6:15 - 7:15 am	Early Riser Yoga Class*		Franciscan C&D	
7:30 - 8:30 am	Breakfast		Exhibit Hall	
7:30 - 8:30 am	ABVP Breakfast for Diplomates		Imperial Ballroom A	
8:30 - 9:20 am	Refining Diagnostic Skills in the Aging Cat: The Sense of Touch	Dr. Bonnie Wright	Continental Ballroom 1-4	zoetis IVAPM
	Comorbidities: Changing the Way We Use NSAIDs	Dr. Dawn Boothe	Continental Ballroom 5-6	
	Technician/Nurse: Hepatic Lipidosis	Ms. Ann Wortinger	Continental Ballroom 7	NAVTA
9:25 - 10:15 am	Tools for Treating OA Pain in Cats Including Concurrent Renal or Cardiac Diseases	Dr. Bonnie Wright	Continental Ballroom 1-4	zoetis IVAPM
	Antimicrobial Risk: Changing Your Approach to Therapy When Comorbidities Exist	Dr. Dawn Boothe	Continental Ballroom 5-6	
	Technician/Nurse: Feeding Tube Management & Complications	Ms. Ann Wortinger	Continental Ballroom 7	NAVTA
10:15 - 10:45 am	Networking Refreshment Break		Exhibit Hall	
10:45 - 11:35 am	Feline Anesthesia: HCM & Other Diseases	Dr. Bonnie Wright	Continental Ballroom 1-4	zoetis IVAPM
	Managing Gastrointestinal Lymphoma in the Diabetic Cat	Dr. Barbara Kitchell	Continental Ballroom 5-6	wedgewood
	Technician/Nurse: Nutritional Management of the Feline CKD Patient	Mr. Ed Carlson	Continental Ballroom 7	KindredBio
11:40 - 12:30 pm	Managing Skin Disease in Cats When Corticosteroids Are Contraindicated	Dr. Catherine Outerbridge	Continental Ballroom 1-4	zoetis
	Managing Concurrent Lymphoma & Heart Disease	Dr. Barbara Kitchell	Continental Ballroom 5-6	wedgewood
	Technician/Nurse: Nutrition for the Hospitalized Veterinary Patient	Mr. Ed Carlson	Continental Ballroom 7	KindredBio
12:30 - 1:45 pm	Lunch		Exhibit Hall	
12:40 - 1:40 pm	*Lunch & Learn #1:** Feline Hypertension: New Developments on a Pressing Topic	Dr. Bianca Lourenço	Imperial Ballroom A	Boehringer Ingelheim
12:40 - 1:40 pm	*Lunch & Learn #2:** Artificial Intelligence Takes the Surprise Out of Chronic Kidney Disease	Dr. Dennis Chew	Imperial Ballroom B	ANTECH DIAGNOSTICS and IMAGING
1:45 - 2:35 pm	Skin Manifestations of Underlying Systemic Disease	Dr. Catherine Outerbridge	Continental Ballroom 1-4	zoetis
	Managing Renal Lymphoma in the Azotemic Cat	Dr. Barbara Kitchell	Continental Ballroom 5-6	wedgewood
	Technician/Nurse: Feline Pain Management: Using Physical Rehabilitation Treatments & Modalities	Ms. Kristen Hagler	Continental Ballroom 7	NAVTA
2:40 - 3:30 pm	Optimal Feline Hydration	Dr. Deborah Greco	Continental Ballroom 1-4	Pro Plan Veterinary Diets
	High Grade GI Tumor With Intestinal Perforation, Spectacular Dysbiosis, & Small Cell Lymphoma	Dr. Barbara Kitchell	Continental Ballroom 5-6	wedgewood
	Technician/Nurse: Lights, Camera, Action: Using & Understanding Therapeutic Laser for Pain Management	Ms. Kristen Hagler	Continental Ballroom 7	NAVTA
3:30 pm	Conclusion of Conference			

*Separate Registration Required. No fees associated.

Refining Diagnostic Skills in the Aging Cat: The Sense of Touch

Bonnie Wright, DVM, DACVAA, cVMA, CVPP, CCRP, CCRT

Introduction

Cats are notoriously challenging to diagnose with internal conditions, such as pain and systemic diseases, due to their tendency to internalize. An inquisitive physical exam can reveal many of these hidden secrets, and when done gently and with respect to the cat, can also benefit the practitioner-cat-and client relationship. While much of this concept is related to locating pain, these tools can be utilized for discovering the somatic footprint of pain or disease that is occurring in other organ systems.

Pain Assessment

Armed with a complete history and a standardized quality of life questionnaire (QOL), the practitioner's most valuable tool is the physical examination. The technique of myofascial palpation in addition to a thorough orthopedic examination can elucidate a vast number of pain conditions that would otherwise be missed, because pain is often much more complicated and multi-faceted than imaging data can reveal. (Ma YT, 2005) Ideally, this examination should be fed into a standardized pain scale, and evaluated at each visit. This is especially important, because pain is seldom static, and will undergo periods of exacerbation and improvement independent of the treatments being instituted.

Examination in cats requires a few comments, and this sort of exam varies from the typical exam performed by veterinarians, which includes a number of different aspects. To differentiate, we will describe this as the myofascial exam. It is vital to pain evaluation that the patient is minimally restrained, and in a comfortable location. A patient that is being held down, is fearful of the examiner, and replete with catecholamines; is unlikely to demonstrate behavioral indicators of pain. These are the most valuable clues available to the veterinarian. A location where the cat can move about on a soft surface, without escaping to a hiding place, is the ideal place to start the evaluation. It often takes significant time, and a willingness to take 'breaks' in order to get a thorough evaluation of a cat for painful conditions. What appears to be a similar condition may have a vastly different level of pain in different individuals, and a gentle, inquisitive exam will help to discern both the regions of pain, and help to direct the application of treatments. A gentle exam will go a long way in your relationship with both the cat and client. As most forms of chronic pain will never completely resolve, this is likely to be a long-term relationship, so having a good relationship is very desirable.

Myofascial exam should have a general aspect, in that *all* of each patient needs to be touched; but it can also have a more specific emphasis. Frequently encountered types of chronic pain in cats include osteoarthritis, dental and gingival disease, neurological pain (especially lumbo-sacral spondylopathy), cystitis, chronic pancreatitis, and ongoing pain from previous surgical procedures- especially declaw or tail injury/ amputation. Surgery causes pain sensing pathways to activate and often amplify, resulting in a surprisingly high incidence of ongoing pain after surgical procedures. The numbers are reported at 10-70% of the human population. (Ma YT, 2005) Furthermore, orthopedic conditions that result in altered kinesthetics will often result in secondary soft tissue pain, and this pain is often the major culprit in causing pain states, often well above and beyond the amount of pain caused by the primary lesion. (Kehlet H,)

Myofascial palpation utilizes the fact that muscle and fascia live alongside the neurological framework and become implicated in pain from various sources. (Berrueta L, 2016) A basic understanding of myofascial trigger points (MTrP's) is helpful to understand the information that can be gained from this technique. The term myofascial trigger point refers to a pain phenomenon of soft-tissue origin that is characterized by two specific attributes: a hardened muscle band (motor dysfunction) that is intensely painful on palpation (sensory dysfunction). With excessive neuronal activity associated muscles spasm and enter an 'energy crisis'. (Donnelly, 2018) Thus, trigger points are painful areas of sustained muscle contraction that cannot easily self-release because of anoxia. The also lead to shortening of muscle groups, and constant traction at the neuromuscular junction- leading to sustained release of acetylcholine (Ach). Trigger points form for a variety of reasons, such as simple strain, prolonged spasm due to compensatory kinesthetics from osteo-arthritis or pain, to the body's attempt to stabilize joint laxity. Once trigger points form, they tend to become self-perpetuating due to the physiology of muscle contraction. Muscles utilize ATP during the relaxation phase. After active ratcheting of the actin heads (allowing muscle relaxation), contraction is actually a non-energy utilizing step. This is the explanation for rigor mortis after hypoxia has set in following death.

In addition to being painful of their own right, MTrPs contribute to changes in movement and put additional strain on joints and/or spinal segments served by the contracted muscle bellies. Over time this 'myofascial restriction' helps to

create co-morbid conditions that accumulate into a multi-faceted pain experience. Trigger points occur in predictable patterns based upon the location of pain or injury that started the cycle. There are textbooks describing the patterns in humans by Travell and Simmons. (Donnelly, 2018) Although not yet described as elaborately in our species, trigger point patterns can be learned through experience. This can help in localizing the origination of pain in cats. Even internal conditions linked to visceral pain can manifest as trigger point patterns, especially in the paraspinal region. (Chen S, 2014)

Regardless of the source of pain, myofascial palpation can generally point in the direction of the problem and remains an invaluable tool for pain diagnosis. Trigger points can be diagnosed by advanced imaging such as EMG or ultrasound, impractical in everyday clinical use. Fortunately, they have a very characteristic feel, pattern of development, and response to strumming or needling. With strumming or needling you will see fasciculation of the muscle group, and frequently you will also see an expression of immediate pain from you patient. Thus, to prevent ruining your relationship with your patient, I recommend a gentle but inquisitive touch. Learning this skill set usually requires taking part in a rehabilitation or chiropractic course, learning from an established practitioner, and it is also taught as part of most medically based acupuncture courses.

The Myofascial Exam

As with other forms of physical exam, it is helpful to progress in a standard order. However, when assessing pain, if a painful region is recognized prior to palpation of this region, it is best to save this region for later in the exam. As the exam progresses the patient generally becomes more calm and accepting of the palpation, as the practitioner makes it clear that they won't push pain beyond the most subtle of recognizable indications of pain (such as ear position, moving away from the palpation, trigger point patterns, and offering a different region in "trade"). Thus, while a person may traditionally start their exams with the head, if there is head or neck pain- this exam should start near the tail instead. As cats are generally allowed to come and go from the exam- this organized description is likely to occur more piecemeal that described.

A typical myofascial exam would start with the head, and include palpation of the temporal groups, masseter groups and TMJ. The spine would be palpated from the cervico-occipital junction through the tail- with separate consideration for paraspinal palpation of myofascial trigger points and discrete palpation of vertebral bodies. Often some attention is paid to more lateral body wall structures if sensitivity is found closer to the spine. Important proximal groups to palpate include trapezius, rhomboid, latissimus and iliopsoas. Pain in these regions can lead to a more meticulous palpation of the associated limb, or where the latissimus is concerned, a more thorough assessment of hindlimb weakness or neurological deficits. Appendicular palpation should also be done in an orderly fashion, and can progress either distal to proximal, or proximal to distal. Joint dynamics can be assessed during the soft tissue palpation or as a second series, and is informed by bony changes, lameness, radiographic changes and heat. Sacro-pelvic pain is a common finding in aging cats, often concomitant with other issues, so this region should receive specific attention during the spinal portion of the exam, or with the pelvic limb assessment.

After combining the information from orthopedic and myofascial exam, history and QOL, and performing relevant diagnostics based on exam (radiographs, CT, MRI, biochemical data, CBC); pain treatment can commence. In general, any condition that is treatable to resolution may not require long-term pain treatment, but will probably require analgesia during the resolution phase. Unfortunately, the vast majority of chronic pain conditions are not curable, but will require ongoing treatment. It is recommended that all pain conditions (acute and chronic) and most chronic medical conditions are treated with a combination of pharmacologic and non-pharmacologic therapies.

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Tools for Treating OA Pain in Cats including Concurrent Renal or Cardiac Diseases

Bonnie Wright, DVM, DACVAA, cVMA, CVPP, CCRP, CCRT

Introduction

Osteoarthritis (OA) is a chronic, degenerative disease associated with pathology of the synovial joint, and is associated with pain of both peripheral and central (maladaptive) origin, inflammation and decreased mobility. OA is the most common chronic painful condition in cats (up to 90% of cats >12 years of age).[i] OA requires long-term treatment, as it is by definition a condition that does not resolve. The treatment of chronic conditions generally requires long-term protocols. Chronic use of medications increases the likelihood of experiencing known side-effects, encountering less known problems related to medication, and resistance to medication administration. This becomes even more relevant when chronic pain conditions such as osteo-arthritis (OA) occur concurrently with other chronic conditions, such as renal, thyroid or cardiac conditions. For this reason, as well as because of the growing database behind improved efficacy when non-pharmacologic modalities are added to the treatment of chronic pain, a combination of pharmaceutical (pharma) and non-pharmaceutical options are needed. This lecture will be paired with a later lecture discussing the non-pharma approaches. Assessment of OA pain in cats is accomplished with client-based questionnaires and activity monitors, in addition to the information gathered from a talented myofascial exam (covered in the previous lecture).

Pharmacological Treatments

For pain in cats include drugs that bind to opioid receptors; serotonin and norepinepherine modifying drugs (SSNRI); anti-epileptics; N-methyl D-Aspartate (NMDA) receptor modifying drugs; Non-steroidal anti-inflammatory drugs (NSAIDs); Sodium channel blockers. Additional, some OA specific options are on the ever-narrowing horizon in cats-to include monoclonal antibody therapies by SQ injection, and intra-articular therapies that encompass a spectrum from age-old (Hyaluronic acid and triamcinolone) to somewhat established (biologicals such as modified plasma or stem cells) to emerging (such as c-fiber ablation techniques and botulinum toxin). Lastly, there are several herbal drugs (to include cannabinoids) and supplements that have a far less robust evidence-base, but are frequently found in feline pain formula, and merit discussion.

Despite all of these options, when choosing therapies it is both desirable and comforting to reach first for the few evidence-informed choices. In cats, this is limited to opioids for short-term, acute or adaptive pain, and NSAIDs for short-term as chronic or maladaptive pain. This is where the conversation begins.

Opioid Medications

Are the cornerstone of acute pain treatment, but they have fallen from favor for treatment of chronic or maladaptive pain.[ii] There are limitations to long-term narcotic use, which include a lack of efficacy data, high frequency of administration, side effects such as mydriasis, inappetence, euphoria, issues of tolerance extrapolated from other species, and the possibility of enhanced pain response from direct activation of the glia by prolonged use of opioids (opioid induced hyperalgesia or OIH).[iii] A very thorough review of opioids in cats for acute pain is available, although of limited value in a discussion of treating chronic pain.[iv]

A few possibilities for longer term use of opioids exist and include tramadol and buprenorphine. Although not classified as a true opioid, tramadol has mild opioid effects in cats primarily from a major metabolite, and also serotonin and norepinephrine modifying effects[v]. Furthermore, tramadol has been shown to decrease the maladaptive, central component of chronic pain from osteo-arthritis, demonstrating that it does not duplicate the neuro-inflammatory effects attribute to opioids in other species.[vi] The increased use of sub-lingual buprenorphine has made long term use of opioids better tolerated by both cats and their human companions.[vii] Although this is an expensive long-term treatment, it may escape some of the side effects of other opioids, including OIH. Furthermore, a long-acting buprenorphine has been formulated, which may provide analgesia and plasma levels in cats for up to 72 hours.[viii] As a partial agonist of the mu receptor, buprenorphine provides analgesia for mild-moderate pain. A concern surrounding long-acting buprenorphine is that if analgesia is not adequate, other opioids are unlikely to be effective until the end of the sustained release period (up to 72 hours). A human-labelled buprenorphine patch is available, but as is commonly found with dermal delivery systems, the uptake is highly variable and thought to be insufficient in cats.[ix]

Opioids are often discarded for treatment of chronic pain and OA, but the data above gives some reason in cats to keep this option open. Furthermore, opioids are generally considered very safe choices for concurrent conditions that often afflict cats, such as kidney disease and heart disease. However, a negative to their use, which although it

remains theoretical in the feline species is gaining traction across all species, is that opioids are linked closely to inflammatory cascades, both generalized and neuro inflammatory.[x]

Non-Steroidal Anti-Inflammatories (NSAIDs)
Are important cornerstones of pharmacological treatment of chronic pain across all species and reduce rather than amplify inflammation. Prostaglandins are implicit in pain processing and amplification, but they also mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone.

NSAIDs reversibly inhibit the enzyme cyclooxygenase, which mediates production of prostaglandins and thromboxane A2. Two isoforms have now been recognized, COX-1 and COX-2, and different drugs provide differential effects at these receptors. In general, drugs with greater COX-2 efficacy are considered safer, as they are less likely to dis-regulate homeostatic mechanisms that protect the gut and kidney, at least in the absence of dehydration or other pathophysiology. An extensive review of this class of drugs and what is currently understood in cats is available. Recently, the piprant drug grapiprant (Galliprant), which is approved for use in dogs, has been used in cats, but is still lacking FDA approval. [xi] This is a drug that antagonizes a single receptor (EP4) of prostaglandin PGE2, providing a more narrowly focused anti-inflammatory effect for OA pain.

A combination of concerns has plagued the long-term use of NSAIDs in cats. One concern is about metabolism delays, and consequent drug accumulation. Drugs requiring glucuronidation often have prolonged elimination times in cats due to their well-recognized deficiency in this enzyme system. Drugs likely to be affected by this include aspirin, rimadyl, and acetaminophen. Other NSAIDS are cleared primarily by oxidative enzymes, such as meloxicam, robenacoxib and piroxicam. These drugs have a more rapid elimination time in cats and become the favored recommendations for chronic use. Kidney disease is the second major concern for use of NSAIDs in cats with chronic pain.

Chronic kidney disease (CKD) is extremely prevalent in aging cats (up to 80% of cats >15 years of age). Combined with the high prevalence of OA in aging cats, adequate treatment of feline pain has been compromised by a fear of NSAID related adverse events. However, the etiology of feline kidney disease is unclear, and data is accumulating that NSAIDs may not be harmful, but in fact beneficial in cats with kidney disease, when hydration status is maintained. [i] In a recent review of the evidence for optimism for the use of NSAIDs in cats with CKD, a list of considerations for the safe and chronic use of two NSAIDS: meloxicam a deracoxib is given. [i] This paper should give some security to practitioners that are shy of chronic NSAID use based on previous bad-press, and the existing black-box warning against chronic meloxicam use imposed by legal council to the drug companies.

Other Oral Analgesics
used in cats have far less evidence than opioids and NSAIDs for efficacy in treating pain. These include psychoactive drugs such as the SSNRIs, TCAs and MAOIs; anti-epileptics such as gabapentin; NMDA antagonists such as amantadine and topically applied sodium channel blockers. Aside from renal excretion, most of these medications are considered relatively safe with concurrent diseases, such as cardiac and renal conditions.

SSNRI, TCAs and MAOIs work by increasing either or both serotonin and norepinephrine in the spinal cord and brain by decreasing their uptake or metabolism. Serotonin and norepinephrine are both major players (along with enkephalins) in descending inhibition from the brainstem. Both ligands can bind to multiple receptors, and their effect on pain is related, in part, to which receptors are bound. This creates a 'use dependent' effect, meaning that both a pro-nociceptive and anti-nociceptive effect can be achieved from either ligand, based on the steady state of the patient at the time. Clinically, this translates into an unpredictable clinical effect on pain control. SSNRIs that have been studied in cats include fluoxetine[xii], amitriptyline[xiii] and clomipramine[xiv]. These drugs are generally directed at behavioral issues, such as urine spraying. The only study looking at these drugs for pain evaluated amitriptyline for interstitial cystitis and appeared effective for the chronic pain associated with this condition. For the most part, clinical use of these drugs for pain conditions is extrapolated from the use of this class of drugs to help treat chronic pain and depression in humans. Due to their variable outcomes, use of these drugs is often trial and error. Serotonin syndrome is a considerable consideration when using these medications. Several medications share effects on the mono-aminergic system, such as gabapentin, tramadol and trazadone. Thus combinations of drugs, or the addition of anesthesia to any of these can create a potentially toxic combination. These considerations are heightened in cats with underlying renal or cardiac disease, as both will influence drug elimination and sensitivity.

Gabapentin is an anti-epileptic that is utilized to treat chronic pain in people. It resembles GABA analogs but does not exert influence on the GABAergic system. Gabapentin appears to interact with a very specific subtype of the Calcium channel complex, specifically the $\alpha 2\delta$ subunit. This subunit appears in increasing frequency with heavy neuronal firing, such as in epilepsy or chronic pain. Gabapentin decreases expression of this subunit, restoring

slower, or more normal firing via the calcium channels. In some studies, gabapentin is ineffective in the absence of amplified serotonin facilitation in the spinal cord. This led to the belief that gabapentin is useful in established pain states, but less likely to help in acute pain. However, many meta-analysis from the human literature have recently shown gabapentin to be opioid sparing and efficacious even for treating acute pain.[xv] There is no data for use in acute pain in cats at this time. Although data is lacking, enough information has now been published on the pharmacokinetics in cats to allow for clinical use of gabapentin.[xvi,xvii] Two studies have failed to show MAC reduction or thermal threshold reduction in cats with the use of gabapentin.[xviii,xix] This is not surprising given the specific mechanism of action of gabapentin, with neither group of cats in these studies having chronic pain. Therefore, the data supporting analgesic efficacy of gabapentin for chronic pain in cats is lacking, but the potential for usefulness is very good, and supported by a large body of clinical use that is encouraging.[xx] Gabapentin is now frequently described for use prior to veterinary visits to reduce anxiety and improve handling.[xxi] Gabapentin requires compounding for use in the cat, as the readily available liquid formulation for use in humans is flavored with xylitol, which is toxic to cats. Because gabapentin has a very large dose range, some practitioners just use a high starting dose, rather than having the drug compounded. Most cats tolerate the compounded drug very well, and side effects are very uncommon, and are generally sedation or mild gastro-intestinal upset, although neurological weakness can be amplified during treatment with gabapentin.

Amantadine is another orally available medication with profile of action that is very attractive for the chronic pain patient. This drug also has a significant N-methyl-D-Aspartate (NMDA) receptor antagonist effect. This is a critical receptor group in amplifying pain signaling, by increasing glutamate flux in the dorsal horn of the spinal cord, and therefore increasing calcium binding and ascending pain impulses. As an oral analog to the drug ketamine, much of the use of amantadine is based on the effect of ketamine on pain states. Much like gabapentin, NMDA antagonists would not be expected to have a significant effect until there was established pain present, as the NMDA receptor is critical in established pain cycles. Both drugs are more accurately viewed as anti-hyperalgesic drugs rather than as true analgesic drugs. The pharmacokinetics of amantadine has recently been described in cats, but a specific dose and dosing interval have not yet been established.[xxii] The dose range being used in practice (2-5 mg/kg orally every 24 hours) has been extrapolated and is without any specific rationale for use in cats. A single study has evaluated thermal threshold reduction in cats, but once again, the population studied did not have chronic pain.[xxiii] As expected, there was not a reduction in thermal threshold with the addition of amantadine to this group of cats. The scientific data supporting the use of amantadine has lagged clinical use. Clinical use of amantadine has been growing, and the drug has been associated with minimal side effects (occasional gastro-intestinal upset) and has been well tolerated. Use of this drug requires rationalizing the implicit discomfort and risk associated with a treatment that lacks robust scientific evidence, but also appears to pose less risk than some of the more-studied drugs.

Sodium channel blockers have a long-established use for nerve blockade, but their use is primarily in the acute peri-operative category rather than for chronic OA pain. A liposomal encapsulated form of bupivacaine has recently been approved for use in cats based upon a declaw model. [xxiv] However, alternate formulation of locals has increased the availability of longer-term administration. In particular, the availability of lidocaine in a transdermal patch has allowed prolonged relief when a local or regional painful region is being treated. Although efficacy work has not been performed for lidocaine patches, safety data is available, and plasma concentrations did not elevate significantly.[xxv] These patches can be cut to an appropriate size and shape for the region being treated, but don't adhere tightly to feline skin. Therefore, some adjustments must be made to increase adhesion, which can cause skin irritation with repeated application. Practically speaking, most feline patients will not leave adhesive items in place, but with the correct patient and creative bandaging, this can sometimes provide an additional tool.

Dietary supplements with some data in cats include green-lipped mussels, glucosamine and chondroitin, omega-3 fatty acids. A recent study evaluating improvement in activity levels and quality of life in cats fed a diet containing these compounds had equivocal results.[xxvi] Owners were very motivated and keen to have the diet improve function, but there was very limited improvement in any objective parameters. Additionally, cat owners feeding the control diet were as likely to report improvement as the group eating the therapeutic diet. Other supplements that are frequently discussed in chat groups and marketed for cats include: Ashwaganda, Boswellia, Myristol, Vitamins A, E and C, arnica, yucca, microlactin and elk-antler velvet. All of these lack robust data, but most have some physiologic rationale for potential efficacy- often relating to anti-inflammatory or anti-oxidant effects. All supplements carry the troublesome feature that cats can be extremely scornful of oral medications. Thus, use of established, evidence-based treatments generally preempts less studied compounds (supplements) when vying for this limited opportunity treatment.

Other Long-Duration Pharmacological Treatments For OA

Include adequan or pentosan injections, joint injections and emerging monoclonal antibody (mAb) therapies targeting pain pathways (such as nerve growth factor- NGF). Polysulfate compounds such as adequan or pentosan, although

never approved for use in cats, have long been appreciated to assist in joint-related discomfort in cats. More recent data has expanded the use to intra-vesicular application during idiopathic interstitial cystitis in cats.[xxvii] Recurrent injections are invariably risky in cats due to their propensity to form tumors at sites of repeated injections, especially with long-acting substances.[xxviii] Thus, efficacy data lacking, the risk of this treatment needs to be carefully weighed in light of the other treatment options available for treating OA pain in cats. Zoetis manages a not-yet-available product that is a mAB for NGF. This product will be given monthly (like cytopoint), and has shown REALLY exciting efficacy in the feline-specific product model. This product shares the feline-specific concern relating to repeat injections, but has the promise of a significant reduction in OA related pain without any negative impact on concurrent chronic conditions, such as kidney disease or heart disease.

Joint injections provide the benefit of a treatment that is almost exclusively LOCALized, which thus limits impact on other organ systems. Joint injections are far more frequently used in human medicine than veterinary, and used in horses>dogs>cats. They have long been accomplished with joint-supporting substances such as hyaluronic acid. Sometimes long-acting steroids are combined with these treatments (triamcinolone having better cartilage-sparing data in equines than methylprednisolone, but there is NO feline data for either). More recently, platelet rich plasma options have become more mainstream, and are associated with excellent intra-articular analgesia in several species (no studies in cats). At the next level of difficulty and cost are stem cells, but thus far the data for stem cells in joints is not superior to the plasma compounds. Furthermore, the stem cells have only been found to increase growth factors rather than become integrated into the joint structures, making the dramatically increased cost compare poorly to expected benefit. And lastly, further down the pike than even the NGF mAb's (perhaps) are some other exotic medications that can be injected into joints to provide long-term relief. At least two of these being studied include resiniferatoxin (to ablate c fibers) and botulinum toxin.

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Feline Anesthesia: HCM & Other Diseases

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Introduction

Whole-body perspectives: The art and science of sedation and anesthesia.

The common impression seems to be that anesthesia and sedation are primarily about the biochemical mediators of these states ("what is your drug protocol for…"). This misses the profoundly important concept that these drugs are acting on a neurochemical substrate that can vary widely, and thus the drug effects may also vary widely.

The goal of both sedation and anesthesia is to titrate anesthetic drugs, dosages and support to maximally accommodate the distinct needs of the individual patient based upon behavior, disease, pain experienced and procedure required. This balancing act cannot always be predicted at the origin of the procedure, so interpreting the consequences of different drugs and actions, and being able to respond definitively to unexpected outcomes requires a good knowledge of both pharmacology and physiology.

Having an appropriately calm patient should be the goal PRIOR to anesthesia, during anesthesia, and in recovery from anesthesia. Thus, sedation and setting are cornerstones of managing the peri-anesthetic window.

Setting involves an attentive and well-trained staff, from the reception desk to the cat-ward. Small and fearful animals should have a safe location, apart from loud, curious and extroverted patients. Patients that are unstable on their feet (elderly, neurologic, ataxic from sedation) should be given good footing and soft options for laying down. Cats should have their own room, away from dogs (with judicious use of feliway). Whenever possible animals should be handled in their comfort zone (on the floor rather than up on metal tables).

Sedation is an end-point, and does not have to be accomplished by a single dose of drugs. It is always dramatically influenced by underlying neurochemical states- such as anxiety, underlying pain, concurrent drugs, and comfort of surroundings. Furthermore, treating known anxious patients PRIOR to their arriving in the hospital is a growing standard of care, and a justified expectation of clients. Many patients remain calmer when allowed to stay with their owners, while others do better separate, if they have a strong need to protect.

Pre-Anesthetic Drug Selection

Justifying use of pre-medications: Patient manageability is a key justification for use of pre-medication drugs. Physiologically speaking, anxiety and pain increase autonomic nervous system tone, which predisposes to adverse anesthetic reactions (arrhythmias, hypotension, apnea, hypoventilation, overdosage, cardiac arrest, poor wound healing). Allowing sympathetic amplification also increases the drug dosages required to attain an appropriate anesthetic state (when taken to an extreme, sometimes a stable level of unconsciousness simply never occurs), and this heightens the negative side-effects of the drugs. Furthermore, tranquilizers are at least additive with general anesthetics, often synergistic, thereby decreasing drug requirements during the maintenance period.

Pain is implicit with most procedures requiring anesthesia- sometimes pre-existing and other times induced during the anesthetic window. In general, pain is most effectively treated prior to initiation (wind-up effect), so even non-painful individuals should be treated with analgesics prior to a painful or uncomfortable procedure.

Finally, the drugs used for pre-medication and anesthesia exert many detrimental effects upon the animal, and some drugs may be used to counter-act these effects. Conversely all premedication drugs have side effects of their own and should be deemed beneficial enough to outweigh the negative aspects of their use. Knowledge of both the beneficial, negative, and perhaps benign but concurrent effects of drugs is a critical step for any person GIVING these drugs- DVM or tech. For optimizing the anesthetic period point-of view, these are the primary drugs (to be covered in more detail in other lectures):

- Pain control: opioids, alpha-two agonists, ketamine, non-steroidal anti-inflammatories and local anesthetics
- Anxiolysis: benzodiazepines, SSNRIs/MAOIs, Trazodone
- Sedation/Tranquilization: Acepromazine, Alpha-two agonists, some opioids, Melatonin, Gabapentin
- Mitigation of anticipated problems during anesthesia: anti-cholinergics, broncho-dilators, anti-arrhythmics, GI motility modifiers

Pre-Anesthetic Exam and History

Sedation/Anesthetic Events, even in emergencies, begin with a thorough pre-anesthetic exam

- Signalment- helps in anticipating potential problems or poor reactions
- History- management, current disease status and treatment, procedure, current medications, behavior
- Temperament- both described by client, and observed. Pre-treat?

- Physical exam- cardiovascular, pulmonary, GI, dermatologic, neurologic, pain
- Laboratory evaluation- age and outcome specific recommendations
- Baseline level of pain- both involved in procedure, and also in other organ systems
- ASA physical status should be reported on each patient to stage risk:
    - I. Healthy and non-geriatric
    - II. Mild systemic disease or advanced age
    - III. Severe systemic disease that complicates anesthesia
    - IV. Severe systemic disease that is a constant threat to life
    - V. Moribund-Not expected to survive without the operation
    - E Emergency event- increases baseline level, regardless of #, by one

Preparation for Anesthesia- Other Steps:
Judicious correction of abnormalities detected as much as possible and within the time available prior to induction of anesthesia. A cost-benefit analysis of performing the procedure and the appropriate time frame in which to perform the procedure should be undertaken in all patients.

1. Rehydration and fluid balance at a level appropriate to maintain cardiovascular stability, but low enough to avoid fluid-overload, edema and consequent poor organ function.
2. Stabilization of progressive conditions such as sepsis, pulmonary, cardiac or cerebral contusions, decompression of bloat or GDV, stabilization of electrolytes in urinary blockage, pneumonia, etc.
3. Hematocrit and clotting abnormalities treated with appropriate transfusion therapy.
4. Preparing the patient for anesthesia with all the information you have gathered

On The Benefit And Cost Of Fasting:
Nausea and vomiting are common during anesthesia induction and recovery, so fasting was previously recommended for at least 12 hours prior to anesthesia. Animals that are sedated or recovering from anesthesia are less efficient at clearing their airways of debris, so vomiting during this time can predispose to aspiration pneumonia. A large stomach volume can also great distention, and with the formation of gas can result in bloat.

However, new data shows that long fasting increases the alkalinity of gastric contents and can contribute to esophageal erosions, or more severe lung pathology if aspirated. The approach to fasting in small animals hasn't reached consensus in light of these new findings. However, a small amount of soft food (a few bites relative to size) has become acceptable up to a couple hours prior to induction. This is can help to provide continuity of medications in patients taking oral drugs (when these are appropriate to be continued through the morning of surgery), and to avoid hypoglycemia. In individuals predisposed to hypoglycemia, fasting is usually eliminated (replaced with small volume of moist food, as mentioned above). This generally includes: neonates, diabetic animals on stable medical therapy. Furthermore, cats on established cardiac medications (amlodipine, benazepril, etc.) should receive the usual cardiac medications on the day of surgery, as these medications have established their current cardiac homeostasis. These can be given with a small bite of food to facilitate medicating and to prevent gastro-intestinal upset from the medication.

Water restriction is not generally advocated in small animal patients, because hypovolemia is dangerous during general anesthesia, and fluid rates are now much lower intra-operatively.

On The Benefit and Cost Of Pre-Anesthetic Handling
Adequate treatment of pain during the pre-anesthetic interval dramatically improves anesthetic stability as well as patient cooperation. Pre-anesthetic handling is one way to detect subtle sources of pain. People have shown reduced pre-medication requirements when given enough time to interview their anesthesiologist, and the same psychosocial need for familiarity may exist in animals with a strong bond. Spend enough time to approach this type of patient reassuringly and avoid unnecessary restraint.
Some patients, however, do better with minimal interaction (wild animals, patients who are fearful of medical providers, fractious cats, etc). Patients that simply cannot handle restraint require one of two possible reactions:

1. Further reliance on oral or trans-mucosal medications prior to arriving at hospital
2. Or they may have to be anesthetized in a less controlled environment (box inductions with inhalant, potent transmucosal, drugs, or IM/darting with potent drugs such as with wildlife)

Reminder:
It is fine for premedication to be a multi-step process (such as oral meds at home, followed by TM meds in the car at the clinic, followed by more TM or other parenteral meds). It is a common mistake to feel 'committed' to a

premedication outcome rather than taking the time to improve it. That said, adding multiple drugs increases the complexity, and can predispose to some forms of toxicity (such as serotonin syndrome).

On the benefit and cost of pre-oxygenation

Any debilitated patient is sensitive to the effects of hypoxemia and should be pre-oxygenated. Furthermore, in any animal that is predisposed to hypoxemia (lung disease, upper airway obstruction, brachycephalic, opioid inductions) pre-oxygenation via a mask is crucial. Anemic patients lack the erythrocyte mass to oxygenate adequately in spite of pre-oxygenation, and should be transfused prior to induction.

High altitude- due to gas laws, resting oxygenation is closer to borderline when practicing medicine above sea level. At higher altitudes, all animals are predisposed to hypoxemia. In my world (Colorado) all small animals are pre-oxygenated prior to anesthetic induction.

Pre-oxygenation via mask should continue for at least 5 minutes in order to attain the peak dissolved gas concentration in blood, to protection against hypoxemia. High flows are needed to overcome the dead space of the mask, and the mask should be left in place for as long as possible prior to intubation.

Contraindication to oxygen? Patient that is currently on fire 

Other costs: struggling with restraint (can compromise mask placement), and time.

End-point goals for safe anesthesia/ chemical restraint?

Calm, comfortable patient

Any consequence of drugs or actions YOU perform, is now YOUR responsibility (monitoring/support)

Maintain or restore: health and quality-based longevity of patient

Enabling future visits to be positive

Personal, staff and client satisfaction

How to Achieve these Goals:

- ***Adjust drug dosages as necessary for your patient- so much of this is experiential… wisdom of practice experience!! Some specifics will be discussed today.***
- All drugs should be dosed to the patient's ideal body weight (with a nod to body surface area)
  In general, larger animals require relatively less drug per body weight than smaller animals. Likewise, older animals require relatively less drug than younger animals.
- Disease and concurrent drug therapy may reduce drug requirements (or increase them!)

Goals of anesthetic drugs: Lack of awareness, analgesia, smooth induction, rapid recovery, maintenance of balanced autonomic reflexes, lack of movement.

Categories of Drugs to be discussed today:

- Pain control: opioids, alpha-two agonists, ketamine, non-steroidal anti-inflammatories and local anesthetics (to be covered in the analgesia lecture)
- Sedation/Tranquilization/Anxiolysis: Acepromazine, Alpha-two agonists, some opioids, benzodiazepines, SSNRIs/MAOIs, Trazodone, Melatonin, Gabapentin
- Suppression of cortical awareness: inhalants, Propofol, Alfaxalone, Ketamine, Etomidate (or sometimes other combinations)
  - Suppression of movement may be covered by these drugs, but neuro-muscular blocking drugs are relevant to this portion of the conversation.
- Mitigation of anticipated problems during anesthesia: anti-cholinergics, broncho-dilators, anti-arrhythmics, GI motility modifiers

Sedation/Tranquilization/Anxiolysis:

The definition of sedation/tranquilization is rooted upon behaviors. However, the definition of anxiolysis is more subjective, and tends to be extrapolated from human studies. I lumped these categories for this reason, as it is difficult for us to assess simple sedation (sleepiness) from a reduction in anxiety. One way this has been studied is by evaluating repetitive behaviors, and it is very possible that anxiety reduction does occur in our species of interest. This is validated by improved survival of wild animals in confinement, improved restraint of horses who exhibit fear (clippers, farrier, twitch, etc.), etc. Of note, there is currently a lively debate on the 'anxiolysis' vs 'hypnosis' associated with some of these medications (acepromazine in particular-with demonization for phobias).

Phenothiazines (acepromazine)
Is the only available anesthetic drug to directly depress activity at the level of the ascending reticular activating system, which is tranquilizing (anxiety reducing, chemical 'straightjacket'?). This provides NO ANALGESIA, and occasionally result in aggression and loss of training. Acepromazine is an alpha-1 receptor antagonist, causing peripheral vasodilation and hypotension. It is CONTRA-INDICATED during hypovolemia, shock, seizures and bleeding disorders or bloody surgeries.

Advantages to Acepromazine Use	***Disadvantages to Acepromazine Use***
	NO ANALGESIA
Tranquilization (anxiety?)	Hypotension from vasodilation (alpha-1 blockade)
Anti-arrhythmic	Lowers seizure threshold (?)
Anti-emetic	Hypothermia: vasodilation and cortical thermoregulation
Anti-histamine (H-1 receptors)	Non-reversible
Vasodilatory	Long duration of action (4-8 hours), slow onset
Potentiate other drugs	Extra-pyramidal effects (tremors, bobbing)
Chronotropic (atropine-like)	Reduced PCV and hemoglobin: platelet effects
	Persistent penile prolapse in stallions
	Occasional paradoxic response: aggression

Minor Tranquilizers:
Benzodiazapines (diazepam, midazolam and zolazepam are in primary use in veterinary medicine: many other derivatives are found in human medicine).

Benzodiazapines are GABA receptor agonists in the central nervous system, decreasing CNS stimulation and activity. They also provide muscle relaxation via internuncial neurons in the spinal cord. They are anti-convulsive and create minimal cardiopulmonary effects. Unfortunately, in veterinary medicine they also tend to be ineffective tranquilizers when used alone in most species, with cats and horses being the most susceptible to excitatory effects. Severe excitation and mania are likely unless the animal is already sedate from disease or other drugs. Thus, these drugs are most commonly use as adjucts to other drugs, either for premedication of ill patients, or to augment induction with most other drugs.

They do provide great CV stability, minimal respiratory compromise, and are thus great adjuvants to other anesthetics. All are highly protein bound, and require hepatic metabolism and renal elimination.
Diazepam is non-soluble and comes formulated in propylene glycol- a vascular irritant. IM absorption is slow and unpredictable. Long term IV administration may result in thrombophlebitis and scarring. Occasional reactions to propylene glycol are reported (hypotension, shock).

a. Midazolam is more potent than diazepam, is water soluble, and may be given by any route.
b. Telazol is formulated with Tiletamine (a dissociative drug) and Zolazepam. Zolazepam is not available as an isolated drug.

Major Tranquilizers:
Alpha-two agonists (and antagonists) Drugs include: Xylazine, Romifidine, Detomidine, Medetomidine, Dexmedetomidine (agonists listed in order of increasing potency). Yohimbine, Tolazoline and Atepamezole (antagonists). These drugs exert agonist activity at central and peripheral alpha-2 adrenergic receptors. Many similarities between the drugs, but some important differences, and both the agonists and the antagonists can have direct peripheral effects on the cardiovascular system. These drugs target alpha-2 receptors of the sympathetic nervous system; which exist both peripherally and centrally. Centrally, cause a decrease NE from adrenergic terminals, inhibit voltage-gated calcium channels (inhibitory), but can also activate phosphor-lipase C (Facilitatory).
Agonists cause sedation, decreased sympathetic activity, analgesia, vasoconstriction, bradycardia, decrease contractility, decrease perfusion. Anticholinergic use to combat bradycardia is not recommended due to protective quality of bradycardia (avoid hypertension, poor coronary perfusion, increased myocardial oxygen requirement and myocardial infarcts). This is especially true for the drugs that maintain vasoconstriction (dex-medetomidine).
Antagonists will reverse sedative and SOME cardiac effects, but do not completely reverse all signs. Use caution when reversing under inhalational anesthesia: occasional unresuscitatable cardiac arrest has occurred (anecdotal). Vasomotor tone is increased due to post-synaptic alpha receptor activity. This is transient with xylazine, but sustained with the more potent agonists.

Advantages to Alpha-2 Agonists	Disadvantages to Alpha- 2 Agonists
Profound, fairly reliable sedation	Profound myocardial depression
Profound analgesia	Elevated vaso-motor tone (variable)
Rapid onset after IV administration	Species-dependent dosing (cattle-pig)
Muscle relaxation	Increase vagal tone and bradyarrhythmias
Marked potentiation of other drugs	Arrhythmogenic- outlasts sedation
Does not produce dysphoria	Coronary artery constriction
Reliable analgesia in horses	Pulmonary vaso-constriction-hypoxia
Reversibility (second drug)	Emesis in cats
	Stimulus-response may occur if used alone (xlazine > dex-medetomidine)

Narcotic (Opioid) Analgesics:
Variety of drugs that bind to G-protein coupled receptors: μ, κ, δ, σ
-μ receptor subtypes mediate supraspinal analgesia, euphoria, dependence, tolerance. respiratory depression (dose dependant), hypothermia, bradycardia, miosis, increased sphincter tone (urinary retention, constipation, pylorus), altered GI motility, vomiting.
-κ receptor subtypes mediate spinal analgesia, sedation and limited respiratory depression.
-δ receptor subtypes are poorly understood, but appear to mediate analgesia, and are recently becoming understood to play a role in cannabinoid/opioid pain modulation.
-σ receptor subtypes are a subject of controversy. These may actually be excitatory subtypes of the μ receptors. In either case, opioids can bind to these receptors to cause dysphoria, hallucinations, tachycardia, mydriasis and mania.

I. Review receptor binding characterisitics:
   a. An agonist is a compound that binds to the receptor and allows full activity of the associated channels.
   b. A partial agonist is a compound that binds to the receptor and opens the channels less than 100%, allowing partial activity.
   c. An antagonist is a compound that binds to the receptor and prevents channels from opening, preventing their activity.
   d. An inverse agonist is a compound that reverses channel flow when bound.
II. Review binding affininty: How firmly a drug binds to a receptor (competitive vs. non-competative)
III. Opioids in clinical use: Many drugs are capable of acting at more than one receptor type. Often this is dose related. The same drug may act as an agonist at one receptor,antagonist at another.

General guidelines for Clinical use of narcotics:

μ Agonist Drugs	potency	**Agonist/Antagonist or Partial Agonists**	potency	**Antagonist**
Morphine	1	Pentazocine	0.1	Naloxone
Hydromorphone	5-10	μ antag/ κ agonist		
Oxymorphone	5-10	Butorphanol	2-5	
Methadone	1-1.5	μ antag/ κ agonist		Naltrexone
Meperidine	0.1-0.5	Nalbuphine	1	
Fentanyl	50-100	Partial μ/ κ agonist		
Etorphine	1,000	Buprenorphine	30	Nalmefene
Carfentanyl	10,000	Partial μ agonist		

Narcotics have a high margin of safety, they cause minimal cardiovascular changes with the exception of meperidine (negative inotrope, histamine release with IV injection), and morphine (histamine release IV). Both of these drugs may cause bronchoconstriction by the same mechanism.

Some individuals may be prone to the dysphoric or manic effects of these drugs. This is seen especially in cats, horses and small ruminants. Within the reduced dose ranges appropriate for these species, narcotics can often still be used effectively.

All opioids are respiratory depressants at high doses. At therapeutic doses most veterinary species are relatively resistant to this side effect. This should be a concern if high doses are used, or if underlying respiratory or CNS disease is present.

Narcotics (morphine, apomorphine) stimulate the chemoreceptor trigger zone and cause vomiting, usually at low doses. This usually occurs before the sedation has occurred, and is less common in patients that are painful. This effect can be reduced by premedicating with a phenothiazine, maropitant or other anti-emetic 20 minutes prior to the opioid, or simultaneously administering a rapidly-acting opioid such as fentanyl (which is highly lipid soluble, so arrives in larger quantities to the CRTZ- therefore exceeding the nausea-producing levels). Narcotics are controlled drugs with abuse potential. They must be logged and carefully monitored. This is increasingly important at this time, due to the opioid epidemic and resulting crack-down on availability occurring in our country.
Narcotics also stimulate glial activation, and contribute to neuro-inflammation, tolerance and dependence. They amplify pain in the long-run, while suppressing pain in the short term. Narcotics cause smooth muscle contraction (initially this may cause discomfort and defecation), ultimately resulting in increased sphincter activity and decreased peristalsis. Urinary retention and constipation may be seen with use (parenteral or epidural). Due to increased spastic peristalsis, endoscopists may have difficulty passing the scope into the small intestine with the use of some narcotics (especially morphine, methadone, fentanyl). Morphine increases venous capacitance: relieving acute pulmonary edema, and contributing to elevations in intracranial pressure. Dysphoria is a common complicating aspect to the peri-operative use of opioids (difficult to discern from pain or emergence delirium).

Most partial and mixed opioids exhibit a ceiling effect on both side effects and analgesia. Increased dosing does not worsen side effects, nor improve analgesia, but will increase effective duration (simbadol in cats). Receptor binding of buprenorphine is extremely avid, so reversal is unlikely.

Opioids undergo hepatic metabolism, bile and urine excretion. Variable duration of action:

Short: fentanyl: 30-60minutes
Meperidine 1-2 hours
Pentazocine 1-2 hours
Nalbuphine 1-2 hours
Naloxone 30-60 minutes

Medium
Morphine 3-4 hours
Hydromorphone 2-3 hours
Oxymorphone 2-3 hours
Methadone 3-4 hours
Butorphanol 2-3 hours (cats)

Long: Buprenorphine 6-8 hours

Oral Sedation Options:
With the growing interest in “Fear Free” clinical practice, oral medications to help provide sedation/anxiolysis are emerging. While we will not have time to go into each of these medications in detail today, these are some of the players:

Gabapentin- 10-20 mg/kg (or 100 mg/cat) can be very sedating until a patient becomes tolerant of this dose. Generally a very safe drug even at high doses, where PK is limited by absorption.
Melatonin- usually combined with Gabapentin or a different oral medication. Dose is extrapolated to be ~1 mg for cats <10#, 3 mg for cats >10#, but this is a very safe supplement, even at high doses.
Trazodone - usually about 10 mg/kg. This drug is a partial antagonist of serotonin in the brain, and also has some SSNRI effects. High doses, or combinations with other SSRIs or tramadol create the risk of serotonin syndrome, which can be severe.
Benzodiazepines- as listed above- oral versions include alprazolam and diazepam. This is not an option for cats, as repeated dosing of benzodiazepines in cats has been associated with hepatic injury. Unreliable behavioral effects also limit the usefulness of this class, although when paired with other drugs they may be efficacious.

Transmucosal drug options: Stand-alone or in combination with oral medications:
Dex-medetomidine, ketamine, buprenorphine, methadone, and to a lesser degree, hydromorphone: have shown some reasonable absorption characteristics in cats.

Mitigation of anticipated problems during anesthesia:
Anticholinergics: Atropine and Glycopyrrolate (historic drug-Scopolamine)

Justification: anticholinergics reduce the effect of the vagus nerve on the heart, increasing heart rate. Pertinent inducers of vagal tone include: opioids, alpha-two agonists, traction on viscera, bladder distention, and many others. Anticholergics also reduce the quantity of inconvenient secretions such as saliva.

Advantages to Anticholinergic Use	Disadvantages to Anticholinergic use
Raise heart rate	May cause bradycardia (transient, or low dose)
Reduce vagal reflexes to retraction of viscera	May cause sinus tachycardia (to threshold)
Reduce vagal tone from narcotics, alpha-2s	Potentiate Ventricular premature complexes
Antisialorrheic	Unpleasant dry mouth in recovery
Inhibits muscarinic effects of anticholinesterases during reversal of NMB	Relaxes lower esophageal sphincter (reflux) Reduces GI motility
Reduces gastric volume and acidity (±)	Inspissates pulmonary exudates (decreased clearance) Decreased efficacy of mucociliary apparatus
Bronchodilation (bronchial diseases)	Bronchodilation (increase dead space)

Characteristics:
Atropine may exhibit a biphasic pattern, initially decreasing heart rate (nicotinic, possibly spinal or central), and then increasing heart rate and AV nodal conduction (from peripheral anti-cholinergic actions). Atropine is well absorbed by any route and has a duration of action from 30 minutes (IV) up to 90 minute (SQ). Atropine is arrhythmogenic, predisposing to ventricular arrhythmias, especially in the presence of high sympathetic tone, hypoxemia, hypercapnia, or other drugs that predispose to catecholamine-induced arrhythmias. At higher than clinical doses, atropine may cross the blood brain barrier and cause agitation, but not glycopyrrolate. Glycopyrrolate is more potent than atropine (2-4 times), does not cross the BBB, and is poorly absorbed SQ. Its duration of action is 4-6 hours, and less increase in heart rate may be noted after its use. Glycopyrrolate may be a more potent antisialorrheic, and the prolonged dry mouth may be uncomfortable after short procedures. Both drugs cause mild bronchodilation and decrease GI motility, an effect that may outlast the other effects by hours. Both drugs predispose to pneumonia by decreasing muco-ciliary clearance in the respiratory tree and increasing the viscosity of respiratory secretions by inhibiting serous but not mucoid secretions.

Atropine	**Glycopyrrolate**	**Scopolamine**
↑ Cross BBB	Does Not cross BBB	↑ ↑ BBB
Biphasic ↑ HR	Mild ↑ HR	Biphas↑HR
↑dose:agitation	No CNS effect (does not cross BBB)	Sedation/anxiety
Arrhythmogenic	Less arrhythmogenic	Arrhythm.
SQ, IM, IV	IM or IV	SQ, IM, IV
Lasts .5-1.5 hrs	Lasts 4-6 hrs	Patch- anti-nausea
.02-.04 mg/kg SA	.005-.01 mg/kg	??
Greater GI stasis	Lesser GI stasis	??
Less antisialogog	More antisialog.	??

Broncho-dilators: Asthmatics. Consider terbutaline 0.1 mg/kg IM, SQ, IV

Anti-arrhythmics:
Cleary differentiate brady-arrhythmias from tachy-arrhythmias!!
Consider lidocaine and/or magnesium for ventricular ectopy/tachy-arrhythmias
Consider atropine/glycopyrrolate for bradyarrythmias and to provide overdrive suppression to some forms of slower ventricular ectopy
Consider anesthesia/analgesia drugs for tachyarrhythmias

GI motility modifiers:
Consider metoclopramide when GI motility is altered. Recognize that most anti-emetic drugs actually DECREASE GI motility. (Cerenia, ondansetron, zolesetron, etc.).

Local Anesthetics:

Pharmacology: Local anesthesia may be produced by a wide variety of drugs and toxins

A. Tertiary amine bases (most clinically relevant local anesthetics)
   1. Aminoamides (NH-C=O) (named with i's in the prefix)
   2. Aminoesters (O-C=O)
B. Alcohols
C. Toxins (wide variety of naturally occurring compounds)
D. Other drugs (cocaine, other opioids, alpha-2 agonists, ± ketamine)

Most clinically useful locals have a tertiary amine and a substituted aromatic ring liked by either an amide or an ester
Lipophilic-Hydrophilic balance depends upon substitutions on the aromatic and ring and tertiary amine

A. The aromatic ring serves as the lipophilic portion
B. The tertiary amine serves as the hydrophilic portion
C. More lipophilic compounds are:
   1. More potent
   2. Produce longer lasting blocks
D. Bulkier (longer latency while drug reaches site of action)
E. Protein binding is favored by moderate lipophilicity. Highly protein bound drugs have increased duration due to decreased removal.

Hydrogen Ion balance determines activity of the drug in vivo, and is dependent upon:

1. The pK_a of the compound. Locals are weak bases that exist in chemical equilibrium between the basic uncharged form [B], and the protonated cationic form [BH^+]
2. The pH of the surrounding media (the more acidic, the more protonated, the less effective the block)
3. The temperature
4. Other environmental factors (the cell membrane, being relatively apolar, tends to concentrate the basic form of the local anesthetic (favoring membrane uptake)
5. The uncharged form is needed to penetrate the membrane, but the protonated form is needed to block the nerve

Formulated as salts in an acidic solution
repeated injections increase the acidity of the medium, and decrease drug effect

Side Effects and Toxicity:

Anaphylaxis: very rare in aminoamides, more common in aminoesters (due to the metabolic by-product PABA)

1. Vasodilation
   A. Sympathetic autonomic fibers maintain vascular tone (c fibres)
   B. Vasodilation may lead to severe hypotension if extensive
2. Loss of motor function
   A. Intentional (regional blocks)
   B. Accidental
      1. Increased spread of drug (epidural or spinal)
         a. Pregnancy tends to decrease epidural space ∴ increasing spread
         b. Rapid injection may increase forward spread of the drug
         c. Excess concentration
         d. Excess volume
3. CNS toxicity (seen before cardiac with most drugs)
   A. Symptoms
      1. Early: tinnitus, lightheadedness
      2. Middle: visual disturbances, muscular twitching
      3. Late: convulsions, unconsciousness
      4. Toxic: coma, respiratory arrest
   B. Accidental overdose
   C. Accidental intravenous administration
5. Cardiac toxicity
   A. Decreased inotropy
   B. Decreased rate
   C. Difficult to reverse
   D. Potentiated by acidosis, hypoxemia

Track A

E. Occurs at 7 times the convulsive dose for Lidocaine, but only 4 times the convulsive dose for Bupivacaine
F. Increased cardiotoxicity in pregnancy
G. L bupivacaine designed to reduce this – but dog study didn't show significant improvement

6 Local tissue toxicity
A. Rarely produce localized nerve damage
1. More common with long-acting drugs
2. More common with added vasoconstrictors
3. Far more likely with high concentrations
B. Chondrotoxicity!
C. Skeletal muscle changes may occur transiently with the long-acting drugs.
D. Tachyphylaxis: prolonged or repeated administration may be associated with a decrease in efficacy of the drug
1. Local acidity due to repeated injection
2. Tolerance
3. Nociceptive dermatome modifications

4. Methemoglobinemia
A. Formed when the ferrous ion (Fe++) in hemoglobin is irreversibly oxidized to the ferric ion (Fe+++)

Nocita:
Liposomally encapsulated form of bupivacaine. Purports a three-day gradual release of active bupivacaine. Approved for stifle surgery in dogs at 5.3 mg/kg and declaw surgery for cats at 5.3mg/kg per limb. This drug does NOT diffuse through tissue plains, so must be injected into EVERY level of surgical incision. Please see website: nocita.aratana.com/ to review technique before use. No other approval yet (all else off-label), but ongoing study for declawing cats (same dose). Note: bupivacaine itself is off-label in dogs and cats- this being the first and only form approved in dogs.

Six hour shelf-life is fairly firm- by 24 hours there is an unpredictable level of free bupivacaine (released after puncturing bottle), and the duration is unknown. Also, do not mix with any other drugs, either in the bottle or in the tissues. Avoid laser after use, but likely acceptable to use ice (but not studied, yet).

Expense (~$180/vial) offset by duration of action (saves 2-3 days of CRIs and in-hospital analgesia)
Y level of surgical incision. Please see website: nocita.aratana.com/ to review technique before use. No other approval yet (all else off-label), but ongoing study for declawing cats (same dose). Note: bupivacaine itself is off-label in dogs and cats- this being the first and only form approved in dogs.

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Premedicate (or restraint)
Between 15 minutes and two hours prior to anticipated surgery time (short for dex-medetomidine, long for acepromazine/trazadone). Opioids vary by drug- morphine, buprenorphine and hydromorphone longer (3-4 hours), butorphanol short (1 hour). If more than 3-4 hours have passed since opioid portion of premedications, the opioid portion should be re-dosed.

1) Opioid - generally a full mu agonist unless the condition is non-painful (x-rays) or fully blocked (small wounds).
2) Consider Sedative- May not be needed for calm or fragile patients
- should be used when safe to reduce anesthetic doses and anxiety and improve recovery
*Gentlest (and also least effective)- midazolam (0.1-0.4 mg/kg)
*Moderate (both non-reversible)– acepromazine (injection 0.01-0.05 mg/kg) or trazadone (2-6 mg/kg oral)
*Most Sedating (also analgesic and reversible)- dexmedetomidine
3) Reserve anticholinergics for as-needed use except as noted under special conditions
4) Note: VERY anxious animals should be given oral sedation before coming to the clinic. This can be drugs such as: Gabapentin, Trazadone, or Acepromazine, and supplement Melatonin
5) Catheters can be placed in non-premedicated patients, but if you choose this route, you should use topical lidocaine to desensitize the skin, and reduce the likelihood of patients becoming fearful on this and future visits. Practice low-stress restraint techniques!!!!!

Induction

Five major options (specific pros and cons under special conditions)- all doses IV and to effect (use lowest end- dose tends to be much lower for more sedated patients (dex-medetomidine)).

1) Alfaxalone IV: 1-2 mg/kg dogs and 2-4 mg/kg cats.
2) Ketamine (5 mg/kg) IV and Midazolam (if used as premed- total dose below 0.4 mg/kg)
3) Propofol (3-5 mg/kg) with or without midazolam (0.1-0.2 mg/kg)
4) Etomidate (1-2 mg/kg) with fentanyl (0.01mg/kg) and/or midazolam (0.1-0.2 mg/kg) (mildest option- does not work well in poorly premedicated, alert patients)
5) Opioids (fentanyl preferred) and Benzodiazepines (midazolam or diazepam) : least reliable

Maintenance

1) Inhalant (either isoflurane or sevoflurane: they are basically equivalent). Run semi-closed systems at ~30ml/kg/min of oxygen and non-rebreathing at 200 mg/kg/min.
2) Local anesthetics in EVERY surgery, wound, etc. (Total dose < 2 mg/kg bupivacaine and 3 mg/kg lidocaine or mepivacaine)
3) When needed to augment inhalant to improve hemodynamics, analgesia and anesthetic plane (limiting ups and downs) the following can be used as intermittent bolus:
    a. Alfaxalone 0.1-0.2 mg/kg
    b. Ketamine 0.1-0.2 mg/kg (diluted 1:10 and given at 0.1 mL/10# and repeated prn)
    c. Fentanyl 3-5 micrograms/kg (0.3 ml/10# and repeated prn)
    d. Dex-medetomidine 0.25- 1 microgram/kg (diluted 1:10 and given at 0.02 ml/10#)
    e.

Recovery

1) Anti-inflammatory if not contra-indicated once blood pressure is stable over 90 mmHg (systolic) without ancillary support
2) Repeat any narcotic doses when nearing the end of their duration of action (morphine 4 hours, hydromorphone 3 hours, butorphanol 1 hour, buprenorphine 6 hours, Fentanyl 20 minutes)
3) Repeat any local blocks that are nearing their duration of action (lidocaine, mepivacaine 2 hours. Bupivacaine 4 hours)
    a. Consider long-acting bupivacaine- Nocita- 3 days duration
4) If using pain infusions, reduce to maintenance levels 15-20 minutes before recovery

Special Conditions

1) Shock patients- stabilize FIRST! Avoid vasodilators (acepromazine, propofol, limit inhalant) and CV depressants (dex-medetomidine and minimize inhalant). Best choices: fentanyl, midazolam, etomidate, fentanyl/ketamine CRI, ketamine low-dose bolus intra-op. If sepsis is likely, definitely avoid propofol (reduces splenic clearance of bacteria)
2) C-section- Avoid dex-medetomidine, ketamine, telazol and midazolam. Best choices: fentanyl (IV for premed but hold infusion until after puppies/kittens are out), propofol, line block of abdominal incision, maintain oxygenation and blood pressure (imperative)
3) Renal patients – avoid CV depressants (dex-medetomidine and minimize inhalant). Imperative to maintain systolic blood pressure over 100 mmHg, but if this is done vasodilators can be useful (low-doses of acepromazine, propofol). No NSAIDS until established in recovery and stable.
4) Liver patients- limit benzodiazepine doses to <0.2 mg/kg (or avoid althogether). Best choices: propofol, fentanyl, lower-dose opioids. Dex-medetomidine is debatable (reversible, but reduces perfusion of the liver).
5) Urethral obstruction- opioid of choice, start IV. Use sacro-coccygeal epidural (under just the opioid if possible- otherwise may need to add sedation or anesthetic). Generally do not need general anesthesia if sick (if anesthesia is needed you must address the potassium first)
6) Non-clinical heart murmurs that you think are mitral- tolerate anesthesia well. Avoid dex-medetomidine, and only consider acepromazine if you can intervene to maintain a good blood pressure. Keep heart rate >60 and utilize dopamine/dobutamine/ephedrine if blood pressures are low (rather than fluid bolus)
7) Clinical low-contractility heart conditions (episode of failure, dilated cardiomyopathy, echo showing declining contractility). Do not use any dex-medetomidine and be very careful with acepromazine, do not induce with ketamine, telazol and avoid propofol if possible. Best choices: fentanyl, midazolam, etomidate. Limit inhalant by using opioids, midazolam, low-dose ketamine. Restrict IV fluids and do not use colloids. Keep heart rate within 10% of starting with atropine or glycopyrrolate to-effect (IV). Be prepared to use positive inotropes.
8) Poor filling heart conditions (HCM, aortic or pulmonic stenosis, restrictive pericarditis). Avoid vasodilation!! Limit inhalant and do not use propofol or ketamine/telazol at induction doses. This is one

of the rare cases where dex-medetomidine, in ultra-low titration, may be beneficial in a compromised patient.

9) Central nervous system/eye (brain trauma, tumor, enucleation). Use opioid but limit dose to low-end. Best choices: midazolam, propofol, glycopyrrolate (0.1mg/kg IM) to prevent avoidable bradycardia. Must ventilate if sedating or anesthetizing to a CO2 of 35 mm Hg on capnograph
10) Pulmonary disease. Consider morphine to decrease pulmonary edema, or butorphanol if respiratory distress appears imminent. Avoid propofol as it limits pulmonary V/Q matching. Avoid anticholinergics as they decrease mucociliary clearance. Avoid dex-medetomidine due to increased cardiac work-load (may already be overloaded from increased pulmonary pressures)

Infusions and Local Blocks to Master:

1) All dental blocks
2) Testicular blocks (and line blocks) for neuters
3) Line blocks/pedicle blocks for spays
4) Coccygeal blocks for urethral obstruction/anal sacs
5) Epidurals or femoral/sciatic blocks for orthopedics (knees)
6) Declaw blocks (nocita)
7) Ear canal blocks for TICA (beware of nocita in the head blocks)
8) Morphine- ketamine CRIs (in bag version- any component can be used)
9) CRIs that are possible but increased care is required when using in-bag instead of syringe pump:
    a. Other opioids than morphine
    b. Dex-medetomidine

NOTES:

NOTES:

Managing Skin Disease in Cats When Corticosteroids Are Contraindicated

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Introduction

Corticosteroids are a commonly prescribed drug class in feline dermatology. They are prescribed for the management of feline allergic dermatitis, or immune mediated skin diseases. Skin disease is a common clinical presentation in small animal practice and the presentation of the feline patient with concurrent systemic diseases that may make the use of corticosteroids contraindicated can be particularly challenging. Cats with concurrent diabetes mellitus, significant cardiac disease or significant infectious disease are examples of feline patients where corticosteroids are likely contraindicated. Prescribing corticosteroids for managing feline skin disease can also be contraindicated if the individual patient has developed significant side effects from prior corticosteroid administration.

Side Effects of Glucocorticoids in Cats

Cats do not absorb or convert prednisone to prednisolone (active form) as effectively as dogs. After oral administration of prednisone in cats only about 21% of the drug can be measured in the blood stream as the active form prednisolone[1]. Prednisolone or triamcinolone are the oral forms of glucocorticoids the author uses most often to manage skin disease in cats, when there is no contraindication for their use. Triamcinolone is more potent than prednisolone and it binds with more affinity to the glucocorticoid receptor, which is associated with the anti-inflammatory potential. Whenever possible repositol corticosteroids should be avoided and oral formulations are preferred, as oral administration allows for more titrated dosing. Whenever prescribing glucocorticoids it is important to be aware of side effects that can occur in cats and monitor for them.

Effects on Immune System

Glucocorticoids are often prescribed because of their effects on inflammation and the immune system. Cell mediated immunity is more impacted than humoral immunity by glucocorticoids and in fact most of the effects on the humoral immune system by glucocorticoids are indirect and result from their effects on antigen presenting cells or T helper cells. Allergen specific IgE was decreased in study cats after they received 2 mg/kg of prednisone for 2 weeks yet IgM and IgA levels were not changed [2]. These immunologic changes provide the desired pharmacologic activity when corticosteroids are used for treating allergic skin disease or an immune-mediated skin disease. However, these effects on the immune system make corticosteroids contraindicated if the cat develops an opportunistic infection.

Effects on Glucose Regulation and Diabetes Mellitus

Glucocorticoids can result in insulin resistance, increase circulating blood glucose levels and, potentially in some cases, lead to overt diabetes mellitus. Glucocorticoids cause insulin resistance through their influence on a number of different pathways. They can increase hepatic glucose production by upregulating an enzyme in the gluconeogenesis pathway in the liver[3], and increase the synthesis of glycogen via effects on hepatic enzymes involved in glycogen synthesis[4]. Glucocorticoids may decrease insulin-mediated uptake of glucose and increase lipolysis with resultant increased concentrations of free fatty acids available for gluconeogenesis[3]. Prednisone has been shown to decrease glucose tolerance in cats[5]. One study showed that an immunosuppressive dose of dexamethasone produced a greater decrease in insulin sensitivity than an equipotent dose of prednisolone[6]. Based on this study dexamethasone would be considered more diabetogenic than prednisolone. Cats should have urine glucose monitored when receiving immunosuppressive doses of corticosteroids and any cat that develops PU/PD when receiving corticosteroids should be evaluated for diabetes mellitus.

Effects on the Cardiovascular System

Glucocorticoid administration in cats has been associated with the development of congestive heart failure in some cats with pre-existing cardiac disease [7]. A study investigating the mechanism occurring to precipitate CHF in cats receiving glucocorticoids found that cats that received methylprednisolone acetate developed an increased plasma volume and a small increase in intraventricular septal thickness[8]. It was proposed that the expansion of plasma volume resulted from the hyperosmotic effect of hyperglycemia[8].

Effects on the Liver

A glucocorticoid-induced isoenzyme of alkaline phosphatase (ALP) has not been demonstrated to occur in cats and the half-life of ALP in the cat is much shorter than in the dog[9]. Consequently, the marked increases in liver enzymes with corticosteroid administration that can be seen in dogs are unlikely to be documented in cats. However, hepatomegaly with histologic changes compatible with a 'steroid hepatopathy' with glycogen deposition have been reported in cats with both spontaneous feline hyperadrenocorticism and cats with iatrogenic hypercortisolemia[10,11].

Effects on the Skin

Glucocorticoids inhibit both keratinocyte and fibroblast proliferation and also collagen synthesis, so they can cause marked atrophy of the skin. These effects are what causes the negative influence on wound healing. In some cases, this atrophic change can result in fragile, tissue paper thin skin that tears readily, often during routine manual restraint, this is termed feline acquired skin fragility. Anagen initiation of the hair follicle cycle is impaired by elevated levels of cortisol so alopecia in areas that have been clipped or areas of wear can be seen, Another cutaneous adverse effect of corticosteroids unique to cats is curling of the distal aspect of the pinna, this is most often seen in cats receiving prednisolone acetate but can also occur with chronic oral formulations of glucocorticoids.

Making the Diagnosis of Feline Allergic Dermatitis

Etiology of Feline Hypersensitivity Dermatitis

Less is known about allergic skin disease in cats than is known in dogs. Similar to what is seen in dogs, feline allergic dermatitis can be attributed to three main categories of allergies, although the accepted nomenclature differs somewhat in the cat. As in dogs, flea saliva hypersensitivity dermatitis (flea allergy dermatitis) and food induced hypersensitivity dermatitis (cutaneous adverse food reaction (CAFR)) are both causes of allergic dermatitis in the cat. The term "non-flea, non-food induced hypersensitivity dermatitis" (NFNFIHD) is increasingly a preferred term rather than feline atopic dermatitis as the pathogenesis in cats for atopic dermatitis is much less clear than in the dog. Recent work has been done that demonstrates that interleukin 31, a cytokine known to induce pruritus in dogs and a target in the dog for therapeutic strategies such as oclacitinib (Apoquel) or Lokivetmab (Canine Atopic Dermatitis Immunotherapeutic or Cytopoint, Zoeits), also triggers itch in cats when a recombinant feline IL31 was administered to research cats[12,13].

Clinical Presentation

There are four common clinical presentations seen in itchy cats with allergic dermatitis. Cats will present with one or more of the following four reaction patterns: 1) head and neck pruritus with self-trauma, 2) self-induced alopecia, 3) military dermatitis and/or 4) cutaneous eosinophilic lesions (eosinophilic plaques, eosinophilic granulomas, and lip ulcers). These cutaneous presentations are most often seen as the consequence of an underlying allergic skin disease but other infectious, parasitic, genetic or neoplastic conditions could result in similar clinical presentations. Consequently, a systematic approach is needed relying on information obtained from history, physical exam findings and dermatologic diagnostics (surface cytology, skin scrapings, Wood's lamp examination) to establish a diagnosis of allergic skin disease. It is critical to determine which categories of allergy are present, as cats can have more than one category of allergy and if there are, unrecognized causes of pruritus the cat will be more difficult to manage successfully and more likely to have increased amounts of corticosteroids prescribed then if all allergic triggers were identified.

Ways to Manage Feline Allergic Dermatitis Without Corticosteroids

Multimodal Management of Allergic Skin Disease

When trying to limit the amount of corticosteroids an individual cat receives in management of their pruritus, an important strategy is to identify all causes of pruritus and follow a multimodal management approach to allergic skin disease to attempt to decrease the summation effect of pruritic triggers that often raises a cat above its pruritic threshold. Identifying and managing for all possible causes of pruritus requires ensuring that all non-allergic causes of pruritus are ruled out; that any possible secondary skin infections with yeast or bacteria are identified and managed, that the cat is screened for possibility of ectoparasites, and that all allergic cats in flea endemic areas receive appropriate flea control. This may mean year round flea control and ensuring that all pets in the household are also on appropriate flea adulticide preventatives. Part of multimodal management of the allergic cat may also include a diet trial with a diet that contains either hydrolyzed protein or a novel protein based on the cat's diet history. This is particularly indicated in the cat with non-seasonal pruritus with marked head and neck pruritus as this distribution is more often associated with CAFR[14]. Diet trials should be at least 8 weeks in length, although 80% of cats based on an evidence based literature review had improvement within 6 weeks[15]. Client education about performing a diet trial is key and at the end of the diet trial possible food protein hypersensitivity is confirmed by eliciting a pruritic flare when the cat is fed its prior diet. Serum allergy testing for food allergens is not recommended as it has been proven unreliable in dogs in several studies[16]. Cats that have both CAFR and NFNFIHD may only have partial resolution of pruritus with a diet trial but will flare when fed their prior diet. The diagnosis of NFNFIHD is one of exclusion by ruling out all other causes of pruritus. If corticosteroids are contraindicated and identifying and managing for all possible pruritic causes fails to sufficiently control pruritus there are a number of other pharmacologic options, allergen specific immunotherapy and future potential biologics that can be utilized..

Essential Fatty Acids and Antihistamines

These are treatment options with inconsistent efficacy; however, they are typically well tolerated, although additional orally administered medications can negatively impact the cat – human relationship. AS histamine is not the only mediator recognized to trigger pruritus and is unlikely in most dogs or cats to be a main one, these would be poor

choices for solo therapies for a cat with severe pruritus. A past study seemed to demonstrate a synergism between chlorphenaramine (2 mg/cat) and an omega 3/omega 6 supplement (0.5ml/cat) as 6/11 cats had an excellent response to this combination when past administration of either medication alone did not result in the same positive clinical response[17]

Cyclosporine

Cyclosporine (CsA) is a calcineurin inhibitor labelled for use in cats since 2011 but has been used off label as an immunosuppressant in cats for decades. Oral administration of the microemulsified CsA in 25 mg gel caps labelled for use in dogs (Atopica, Novartis) or the100mg/ml liquid formulation labelled for use in cats (Atopica for Cats, Novartis) at 7 mg/kg daily to every 48hrs are the author's preferred formulations. Cyclosporine is too large a molecule to be successful absorbed with transdermal formulations. There is one study reporting subcutaneous administration of cyclosporine for management of pruritus[18]. An open pilot study reported the subcutaneous administration in 11 cats with NFNFIHD of 2.5 to 5 mg/kg of CsA (Sandimmune 50 mg/ml) every 24 to 48 hrs[18]. Six cats showed clinical improvement and 2 in the study developed injections site reactions[18].

Cyclosporine effects predominantly cell mediated immunity inhibiting T cell proliferation and activation by decreasing interleukin-2 (IL-2) as well as a number of other interleukins and cytokines[19]. Absorption and metabolism of cyclosporine is variable between individual animals and drug levels are also influenced by interactions with other drugs, as CsA is metabolized by cytochrome P450 enzyme system and is a P-glycoprotein substrate and inhibitor[18]. Ketoconazole, itraconazole and clarithromycin can all increase CsA levels and doses need to be adjusted when these drugs are used concurrently[20, 21]. The product insert states that CsA is contraindicated in cats that are positive for feline retroviral infections and in cats with a history of malignant neoplasia and it is not recommended for use in cats with diabetes mellitus. There is no data on its safety in cats less than 6 months of age, under 2.3 kg in weight or in breeding, pregnant or lactating animals. The most common adverse effects seen in cats are gastrointestinal signs of vomiting and soft stool. These side effects are often transient and may dissipate over several weeks. Weight loss and hyporexia have been documented in cats receiving CsA, but these signs resolved with dose reduction[22, 23]. Gingival enlargement due to increase in extracellular matrix by fibroblasts has been documented to occur as a rare side effect in cats, as has an acute bullous keratopathy[24,25]. An increased risk for development of malignant neoplasia has been associated with the doses of CsA used in feline transplant medicine, this appears to be a rare event in cats receiving CsA at doses administered for managing skin disease[22]. Opportunistic infections can develop in cats treated with CsA. Most concerning is the development of fatal toxoplasmosis. Serologic testing for toxoplasma before starting CsA can be done but most important to minimize toxoplasmosis risk is that treated cats are kept indoors, and not fed raw meat. Monitoring drug levels is not useful in evaluating therapeutic efficacy but is utilized to identify at risk cats with high CsA levels so that dose reductions can be undertaken to minimize risk for opportunistic infections[26].

Cyclosporine is prescribed for the management of chronic allergic dermatitis, as it will take 2 to 3 weeks to have maximum effect it is not a good rescue drug for cats experiencing significant pruritus needing immediate relief. The drug has also been used in the management of feline pemphigus foliaceus and a variety of other immune mediated skin diseases. The author has used CsA to try and treat a number of immune mediated skin diseases in the cat including: feline urticarial pigmentosa (mastocytosis), degenerative mucinotic mural folliculitis, alopecia areata, idiopathic facial dermatitis of Persian cats, plasma cell pododermatitis, and exfoliative dermatitis not associated with thymoma.

Allergen Specific Immunotherapy

Cats can be tested to determine what should go into allergen specific immunotherapy (ASIT). Serum allergy testing is done more frequently than intradermal testing (IDT) but some cats do develop strong reactions on an IDT. So if the serum allergy testing provided insufficient information to customize ASIT having the cat undergo IDT could be considered if ASIT is a desired therapy to pursue. Regional Specific Immunotherapy (RESPIT®) could also be considered, with this form of immunotherapy allergy testing is not done but the most common allergens found in various geographic regions are utilized. ASIT can be delivered as subcutaneous injections or oral drops (sublingual immunotherapy (SLIT)). Immunotherapy is a therapy to consider for chronic management of non-flea, non-food induced immunotherapy and not immediate relief as it will take several months to have an effect.

Oclacitinib

This drug is not approved for use in cats. As a Janus Kinase -1 (JAK-1) inhibitor oclacitinib (APOQUEL, Zoetis), in the dog, blocks JAK-1 dependent pro-inflammatory cytokines including the pruritogenic cytokine interleukin 31 (IL-31), and consequently it decreases pruritus and improves lesions associated with allergic dermatitis. Without causing the side effects seen with glucocorticoids, oclactinib has a similar efficacy at decreasing itch in dogs compared to prednisone[27, 28]. There have been several studies in cats looking at the effects of oclacitinib. A dose of 0.4 mg/kg

was shown to decrease IL-31 induced pruritus in an experimental feline model[12]. A clinical study done using 0.4 to 0.6 mg/kg oclacitinib every 12 hours for 2 weeks in 12 cats controlled pruritus in < 50% of the cats[29]. Another double-blinded randomized study on the efficacy of oclacitinib using methylprednisolone as the control showed that 70% of cats receiving 0.7 -1.2 mg/kg oclacitinib every 12 hours for 28 days had > 50% reduction in pruritus, while 75% of the cats receiving methylprednisolone 0.5 to 1 mg/kg twice daily for 28 days had >50% reduction in pruritus[30]. If oclacitinib is to be used off label to try to manage pruritus in a cat the more effective dose seems to be 1 mg/kg every 12 hours.

Maropitant

Maropitant (Cerenia, Zoetis) is a neurokinine-1 receptor agonist, (NK-1R) which is labelled for the prevention of emesis and motion sickness in cats. One study (open label uncontrolled study) looked at cats with nonseasonal NFNFIHD treated with 2 mg/kg PO every 24 hours for 4 weeks[31]. Based on this 12 cat study the investigators concluded that maropitant was an effective well tolerated therapeutic to manage pruritus as 83% of owners judged efficacy and tolerability as excellent to good. However, there are no long-term studies for safety and no clinical pathology data was obtained during the study.

Monoclonal antibody therapy

Based on the success of a monoclonal antibody against canine IL-31(Lokivetmab/Cytopoint, Zoetis) the future development and marketing of a monoclonal antibody against feline IL-31 would be a powerful tool in the management of pruritus in cats, particularly those cats that have concurrent disease that make corticosteroids contraindicated or that are difficult to administer oral medications. Several possible feline 1l-31 monoclonal antibodies have been developed and an in vivo study with one monoclonal demonstrated its efficacy at controlling pruritus in a feline research model of Il-31 induced pruritus.[12]

Immune Mediated Skin Disease

Pemphigus Foliaceus

The most common immune mediated skin disease in the cat is pemphigus foliaceus. Cats typically present with symmetrical crusting lesions on the pinna, face, feet and lesions can be generalized. A recent retrospective study of 47 cases found that over 90% of cats had lesions involving the pinnae, head and haired face[32]. Clinical lesions and cytology are important to aid in the diagnosis but biopsy of representative lesions is needed to allow histopathologic confirmation of the diagnosis. Corticosteroids are the most commonly prescribed drug to manage feline PF and in the recent retrospective study remission was achieved in the majority of cats with corticosteroids alone[32]. In cats if corticosteroids are contraindicated or not tolerated CsA is a good option. Other immunosuppressives that can be considered include chlorambucil or mycophenolate mofetil. Occasionally localized disease might be able to be managed with topical corticosteroids.

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Skin Manifestations of Underlying Systemic Disease

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Introduction

The skin's functions in providing innate protection and maintaining homeostasis along with the systemic factors that can influence its integrity make it a critical sentinel for systemic disease. Some cutaneous changes are so intimately associated with a particular underlying organ dysfunction or disorder that they are immediate visual clues to evaluate for specific diseases. For example, the color change seen in an animal with icteric mucous membranes is a clear indicator to evaluate for causes of jaundice in that patient. Changes in the appearance of the skin may be markers of pathology occurring in another organ system or they may represent a disease process that is multi-systemic, such as seen with some infectious diseases or in systemic lupus erythematosus. A number of systemic factors influence both the appearance and integrity of the skin. These factors include nutritional status, hormonal levels and interactions, perfusion and vascular integrity and the overall health and systemic organ function of the individual animal. Consequently, changes in the skin can be a critical sentinel for systemic disease. The skin is also readily accessible for diagnostic sampling and in some cases can provide the necessary information for making the diagnosis of a particular systemic disease. Recognizing those skin changes that are clinical markers for underlying systemic disease can expedite the diagnosis and timely management of those diseases.

Cutaneous Changes Associated with Hormonal Disturbances

Endocrine diseases provide excellent examples of the connection between disease and the skin but the most common endocrinopathies in the cat, hyperthyroidism and diabetes mellitus, often have nonspecific changes in coat quality. There may be varying degrees of alopecia and disturbances in cornification due to altered metabolism or secondary to poor grooming in an unwell cat. Acromegaly from excessive growth hormone and disturbances in sex hormones, other than progesterone (see acquired skin fragility and xanthomas); rarely cause any skin changes in the cat.

Thyroid Hormone

Thyroid hormones are very important to the skin and promote the initiation of the anagen phase of the hair follicle cycle[1, 2]. Hypothyroidism results in disturbances in cornification, an increase in the number of hair follicles in telogen and accumulation of glycosaminoglycan in the dermis[2, 3]. Clinically, this results in alopecia, a dull, dry hair coat, variable hyperpigmentation, scaling, and myxedematous changes. The normal barrier function of the epidermis is likely impaired in hypothyroid animals and in animal models, impaired neutrophil and lymphocyte function has been reported. Consequently, recurrent pyoderma and otitis externa can occur in hypothyroid animals[3].

Spontaneous hypothyroidism in cats is rare. One reported case had similar clinical signs to dogs with a dull dry, hair coat that was lighter in color than normal and the cat had a puffy face[4] but experimentally thyroidectomized cats did not; they reportedly groomed less, developed matting and seborrhea but only focal alopecia on pinnae and pressure points[3]. A recent study identified seven cats with spontaneous hypothyroidism with six having bilateral goiter and four had hair coat changes[5]. Hyperthyroid cats can develop matting, seborrhea, increased shedding and over-grooming[3]. With chronicity, alopecia may develop with hypotonic, thin skin[3].

Glucocorticoids

Excessive glucocorticoids cause cornification abnormalities, inhibit fibroblast proliferation and collagen production and cause pilosebaceous gland atrophy. Clinically, excessive cortisol (endogenous or exogenous) also results in disturbances in cornification, dermal thinning and delayed wound healing. Naturally occurring hyperadrenocorticism is rare in the cat and skin lesions have been seen in about half of the reported cases these include alopecia, thin skin, increased susceptibility to bruising, scaling, comedones and fragile skin[6].

Acquired Skin Fragility

Acquired skin fragility in cats is associated with hyperadrenocorticism (more often in those with adrenal tumors), iatrogenic hyperglucocorticoidism, or excessive levels of progestational compounds from either adrenal tumors or the iatrogenic effect of administered progestational compounds. Affected cats have extremely thin, fragile skin that easily bruises and can be torn with simple manipulations, often during restraint or handling. There are also rare reports of feline skin fragility being associated with hepatic lipidosis and hepatic neoplasia[5].

Cutaneous Paraneoplastic Syndromes and Metastatic Skin Disease

A paraneoplastic syndrome is defined as either a disease or clinical signs or symptoms that develop distant from the site of a tumor and these signs are caused by the presence of the tumor or its metastasis, but are not resulting from

the local presence of neoplastic cells. Paraneoplastic syndromes are often mediated by hormones, cytokines or growth factors released by tumors or as an immune response targeted against the tumor. The term paraneoplastic is thought by some to be an inappropriate term to use if the clinical signs are associated with neoplastic tissue producing more of the same substance it normally produces. Consequently, either diseases such as hyperadrenocorticism caused by an adrenal tumor or pituitary tumor is not considered paraneoplastic, although some review papers may cite it as an example. Paraneoplastic skin diseases represent a group of skin disorders that if recognized alert the clinician to underlying internal neoplastic disease. These syndromes are seen most commonly in middle-aged to elderly individuals.

Feline Paraneoplastic Alopecia
This rare, yet highly characteristic skin disease occurs in association with pancreatic adenocarcinoma. Affected cats develop precipitous, ventrally pronounced alopecia in which the skin appears very shiny and smooth but is not fragile. Some cats may also have dry, exfoliative, and shiny footpads often with concentric circular rings of scale. On necropsy, exocrine pancreatic adenocarcinoma with hepatic metastases is the most common tumor found but bile duct carcinoma has been reported in two cases[7]. The disease affects older cats and the chief clinical complaint is often the acute and dramatic alopecia that affects the ventral trunk, medial aspects of the limbs and the ventral cervical region but can generalize. Remaining hairs will epilate easily. Secondary *Malassezia* infections are common and may contribute to why some affected cats groom excessively, potentially exacerbating the alopecia. Skin biopsies histologically reveal epidermal hyperplasia with marked follicular and adnexal atrophy. Any cat with a tentative diagnosis of paraneoplastic alopecia should undergo an abdominal ultrasound to evaluate for the presence of a pancreatic or hepatic mass. Temporary resolution of the cutaneous disease was reported in one cat after the primary pancreatic tumor had been removed; the lesions recurred with progression of metastatic disease[8].

Feline Thymoma-Associated Exfoliative Dermatitis
A rare, exfoliative dermatitis has been described in middle aged to older cats with thymomas[7]. The exact pathogenesis is not known but is thought to be an immunologic etiology potentially T cell mediated. Histologically it is similar to an erythema multiforme or graft versus host type of reaction. Skin lesions tend to begin on the head and pinnae but can quickly generalize to involve the entire cat. Generalized erythema and marked scaling are present. Secondary infections with bacteria and *Malassezia* may develop. Respiratory signs secondary to the cranial mediastinal mass may be present at the time of presentation but in most cases, skin changes precede any other systemic signs. Histopathology of representative skin lesions reveals a cell poor, hydropic interface with apoptosis (single cell necrosis) of basal cell keratinocytes. If detected and diagnosed, removal of the thymic tumor will lead to resolution of the dermatologic clinical signs[7,9,10]. A recent report describes a group of cats that had clinical and histologic features of this exfoliative dermatitis but had no concurrent thymoma; the cats were managed with immunosuppressive medications[11].

Metastatic Lesions from Pulmonary Adenocarcinoma
Primary pulmonary adenocarcinoma in cats can metastasize to the distal phalanges of digits. Cats will sometimes present with digital swelling or lameness. Typically, multiple digits on different paws are affected. Cats may have no respiratory signs so it is important to obtain thoracic films in all cats with digital lesions.

Cutaneous Manifestations of Nutritional or Metabolic Perturbations
The skin can develop lesions secondary to nutritional deficiencies, however this is very uncommon in a patient that has a good appetite and is eating a well-balanced commercial food. Some cutaneous manifestations of nutritional deficiencies are recognized in particular breeds suggesting perhaps an alteration in absorption or metabolism while others have been linked to inadequate or unbalanced diets. Superficial necrolytic dermatitis can be a paraneoplastic skin marker if associated with glucagonoma but it is more commonly associated with some yet to be determined alterations in metabolism that causes depletion of amino acids. Underlying disturbances in lipid metabolism can result in the development of cutaneous xanthomas.

Cutaneous Xanthomas
Cutaneous xanthomas are rare and occur when there is an underlying hereditary defect in lipid metabolism, or acquired dyslipoproteinemia secondary to diabetes mellitus, or use of megestrol acetate. These skin lesions result from the accumulation of lipid-laden macrophages within the dermis. Feline cutaneous xanthomas may develop in cats with hereditary hyperchylomicronemia, megestrol acetate induced diabetes mellitus or naturally occurring diabetes mellitus. Apparent idiopathic cases of xanthomas with no identifying underlying metabolic or hormonal disturbance have been reported. Often, affected animals are consuming a diet rich in fats or triglycerides at the time they develop lesions.

Clinically, cutaneous xanthomas present as multiple pale yellow to white plaques, papules or nodules with erythematous borders. They are often located on the head, particularly the preauricular area or pinnae. Lesions can

develop in paw pads and over boney prominences on limbs Lesions may bruise readily and larger masses may in rare cases ulcerate and exude inspissated necrotic material [12]. Cats with inherited hyperchylomicronemia may also demonstrate peripheral neurologic signs due to nerve compression from subcutaneous xanthoma formation. Histologic evaluation of skin biopsies reveals large foamy macrophages and giant cells. Serum biochemistry evaluations for diabetes mellitus, hypercholesterolemia and hypertriglyceridemia should be obtained. Feeding of a low fat diet and identification and correction of the underlying disturbance in lipid metabolism is recommended for patients that have had cutaneous xanthomas identified.

Vitamin E deficiency: Pansteatitis
Pansteatitis is associated with diets that are low in Vitamin E and high in polyunsaturated fats. A diet comprised entirely of raw oily fish is a classic example. Cats with pansteatitis develop firm, painful swellings associated with the subcutaneous inguinal and abdominal fat pads. The swellings result from the inflammation associated with the peroxidative damage of adipose tissue. Cats may be painful and reluctant to move, anorexic or febrile. It is important to differentiate this disease from panniculitis caused by infectious agents such as the opportunistic mycobacteria that can often cause nodular lesions on the ventral abdomen. Diagnosis is made based on supportive history and histologic evidence of steatitis on biopsy. Biopsy reveals lobular panniculitis with macrophages and giant cells and there is ceroid within lipocytes. Correcting the dietary deficiency and vitamin E supplementation will improve clinical signs.

Cutaneous Manifestations of Systemic Infectious Diseases
Sometimes the skin provides valuable clues to underlying infectious disease. Skin lesions can develop in association with systemic infectious disease. In cats systemic mycosis and a number of viral diseases can have cutaneous lesions develop because of the underlying systemic infectious disease, Sometimes, in these diseases the organism can be found within the lesional skin. Infectious diseases can also cause skin lesions if there is systemic vasculitis or thrombocytopenia that may occur in association with the infectious disease, example feline infectious peritonitis (FIP)

Systemic Mycosis
Many systemic or deep mycoses (blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, aspergillosis and in some cats sporotrichosis) can present with cutaneous lesions along with clinical signs referable to infection in other organ systems. These skin lesions include papules, nodules, draining tracts and ulceration that result from hematogenous dissemination of the fungal organism to the skin or depending on the fungal species direct inoculation of fungal organisms into a cutaneous wound. Skin lesions are seen most commonly in feline cryptococcal infections and sporotrichosis. Typically, there are other systemic clinical signs. Diagnosis of any of the fungal infections is based on demonstration of the organism within biopsied tissue and/or fungal culture. Suspicious cutaneous lesions can provide easy and rapid diagnostic information in the evaluation of animals with systemic mycoses. Appropriate antifungal therapy is chosen based on type of organism and overall health of the animal.

Systemic Viral Diseases
A number of viral diseases cause cutaneous lesions as well as systemic clinical signs. These include in cats the retroviruses FeLV and FIV, feline herpesvirus, feline calicivirus, and feline coronavirus causing FIP. Feline papillomavirus cause cutaneous lesions and not systemic disease but they can develop more readily, become more severe or difficult to manage in patients with underlying immunosuppression.

Opportunistic skin infections, oral ulcerations and gingivitis have been associated with FeLV and FIV. Cutaneous horns can develop on the paw pads of cats with FeLV. In severe cases, lameness and discomfort can be marked. Diagnosis is confirmed with a positive FeLV status and skin biopsy. Immunohistochemistry can demonstrate the presence of the virus within a skin biopsy. Cutaneous lymphoma and giant cell dermatosis have also been reported in FeLV positive cats[13].

Feline herpesvirus ulcerative dermatitis typically involves the dorsal muzzle but lesions may extend to involve the nasal planum. Cats do not have to have concurrent ocular or upper respiratory tract signs. Histologically the lesion is a necrotizing, ulcerative dermatitis most often with a concurrent marked eosinophilic inflammation, but the inflammatory pattern may be strongly neutrophilic in some cases. The presence of eosinophilic inflammation and the clinical appearance of the lesions make it difficult to differentiate from mosquito bite hypersensitivity or other feline eosinophilic ulcerative lesions. Unless intranuclear viral inclusions can be identified, it is not possible to diagnose definitively the virus as the etiologic agent for the ulcerative dermatitis. Polymerase chain reaction (PCR) has been shown to be a sensitive test to detect the presence of the virus within skin biopsies[14]. Treatment can include subcutaneous administration of alpha interferon (1,000,000 units/m^2, 3 times a week), oral famciclovir (Famvir, Novartis Pharmaceuticals) (60-90 mg/kg) [15], and/or lysine.

Vascular Disease
Vasculitis can occur as a primary disease but is more commonly secondary to some other underlying disease process such as an infectious disease, neoplasia, immune-mediated connective tissue diseases or adverse drug reactions. There are both immunopathogenic and non-immunopathogenic mechanisms that can induce vasculitis. Non-immunopathogenic mechanisms that are involved in vasculitis cause disease without primary attack on components of the vascular wall. These mechanisms include invasion of the vascular wall with neoplastic cells or microbial agents and influences of burns, trauma, endotoxin or hemodynamic factors on the integrity of the vascular wall. Immunopathogenic mechanisms for vasculitis include in situ formation or deposition of immune complexes, antibodies directed against vascular wall components, anti-neutrophilic antibody-mediated vessel damage, cytotoxic T cells directed against vascular components and cytokine induced mechanisms.

Vasculitis may involve only one organ system such as the skin or may involve multiple organ systems and consequently the clinical signs can be variable. Cutaneous vasculitis typically results from small vessel vasculitides with lesions of swelling, erythema, hemorrhagic macules, plaques or bullae. Ischemic necrosis and ulceration are often present in lesional areas often located on extremities or over pressure points. Footpads if affected often have depressed areas of central pallor.

Perhaps the most important information to ascertain when evaluating a patient with vasculitis is the possibility of an underlying infectious etiology. If an infectious etiology is not identified, the clinician needs to evaluate for exogenous or endogenous antigens that may be triggering the vessel inflammation. In one study, greater than 50% of the cases were deemed to be idiopathic[16]. If an underlying antigenic trigger cannot be identified, the vasculitis should be described based on pathologic evaluation of vessel type, size, location and inflammatory infiltrate. Histopathologically, vasculitis is often characterized by neutrophilic nuclear debris so called leukocytoclasia, inflammatory cells within the vessel wall, fibrinoid necrosis of vessels and extravasation of RBCs into the surrounding dermis.

Feline vasculitis has been reported as an adverse consequence of drug administration and there are reported cases implicating carbimazole, fenbendazole and oral cimetidine as drug triggers[17, 18]. Viral infection with feline coronavirus progressing to FIP has been reported to cause cutaneous vasculitis lesions[17].

Therapy is dictated by identifying underlying triggers. Infectious etiologies need to be treated appropriately, possible inciting drugs should be discontinued, underlying diseases need to be identified and immunosuppressive or immunomodulatory therapy may be warranted.

Autoimmune Skin Diseases Associated with Systemic Disease
Autoimmune skin diseases are uncommon skin disorders and are reported to account for less than 2% of all skin diseases seen in small animal practice[19]. They are often clinically impressive and can even be life threatening. Definitive diagnosis cannot be based solely on clinical impression or appearance of lesions, and requires timely biopsy of representative samples.

Systemic Lupus Erythematosus (SLE)
SLE is a multi-systemic autoimmune disease. Skin disease occurs variably with percentages as high as 40 to 50% of cases of SLE having skin lesions[19]. Fever, polyarthritis, protein-losing nephropathy from glomerulonephritis, anemia, and thrombocytopenia are the more common clinical signs seen with SLE. Organ specific and non-organ specific autoantibodies target a variety of tissue antigens in SLE. Resultant tissue damage occurs when there is immune complex deposition (as occurs in glomerulonephritis) or can occur because of direct cytotoxic effects or cell-mediated immunity.

Cutaneous lesions are variable and can include erythema, scaling, crusting, depigmentation, alopecia and ulcerations. Lesions may be present on mucocutaneous junctions and within the oral cavity. Ulcers and erosions are rarely diagnostic lesions to biopsy, as an intact epidermis is needed to make a definitive diagnosis. The histopathologic findings are variable but classic lesions include apoptosis of basal cells and basal cell vacuolation, which lead to dermal-epidermal separation and consequent ulceration.

There are published criteria for the diagnosis of SLE in dogs and definitive diagnosis requires the presence of four or more criteria[19]. These criteria include identification of immune-mediated disease targeting various organs systems/tissues +/- a positive ANA. It is difficult to know if these criteria could be applied to cats as there is much more limited data about this disease in this species and some published cases may be probable rather than definitive SLE. Systemic lupus erythematosus is a progressive disease and evidence of immunologic involvement in multiple organ systems may not always be evident on the initial presentation. A thorough systemic evaluation including a complete blood cell count, serum biochemistry, urinalysis, +/- protein to creatinine ratio, antinuclear antibody (ANA),

arthrocentesis and evaluation of joint fluid cytologically may be indicated in patients suspected of having SLE. Most patients with SLE have an elevated ANA although this may not always be present.
Prognosis depends in large part on the organ systems involved. Immunosuppressive therapy with corticosteroids with or without other immunosuppressive drugs (chlorambucil (Leukeran), cyclosporine (Atopica)) is utilized.

Erythema Multiforme (EM)
The terminology has been, over the years, confusing in both human and veterinary medicine in regards to EM and Steven-Johnson's syndrome /toxic epidermal necrolysis (SJS/TEN). It has been documented in human beings that the cell-mediated immune response in EM has a Th 1 pattern[20]. The exact mechanism has not been proven in cats but a T cell-mediated response directed at keratinocytes is most often proposed resulting in apoptosis (single cell necrosis) of keratinocytes. There is a report of EM in which herpesvirus has been implicated in the cat[21]. In humans, EM is highly linked with herpes viral infections.

Lesions are often pleomorphic with an acute onset of erythematous plaques and macules that often become annular or serpiginous as they coalesce or they may appear targetoid. Progression to ulcerations is common and lesions may become variably crusted. Lesions are often generalized but are most commonly found on the ventrum, axillae, inguinal region, mucocutaneous junctions, oral cavity and pinnae. Biopsies should be obtained from areas of erythema without ulceration or crusting as an intact epidermis is needed for the diagnosis. Histologically, apoptosis with lymphocyte satellitosis is the characteristic microscopic lesion of EM.

Prognosis for EM depends on the severity of the disease and identification of underlying triggers. Use of immunosuppressive drugs in human medicine is controversial as EM is often induced by herpes simplex virus[17]. In veterinary medicine, EM patients should be evaluated for underlying triggers: drugs, infection or neoplasia. Erythema multiforme minor may resolve on its own but more severe cases are often treated with immunosuppressive therapy with glucocorticoids with or without other corticosteroid sparing immunosuppressive drugs (azathioprine, cyclosporine, chlorambucil). Severe generalized mucocutaneous EM (EM major) often requires aggressive supportive care in addition to removal of underlying triggers and immunosuppressive therapy.

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NOTES:

Optimal Feline Hydration

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Water and Fluid Balance

Water is the predominant component (70%) of most body tissues, and the most important nutrient necessary to sustain life and all biochemical and metabolism activities. {Greco, 1998} Water accounts for 60-70% of body weight in both cats and dogs; therefore, it is the most important and abundant nutrient in the body. Water serves many physiological functions including transport of nutrients, lubricant, metabolic functions and elimination of waste products through the kidneys. Therefore, hydration is the most important physiological parameter that governs delivery of key nutrients to the body.

Regulation of Water Balance

There are two main fluid regulatory processes for water balance, drinking and urinating. Drinking responds to signals of water deficit which results in the stimulation of thirst. There are two main mechanisms of physiological thirst: the intracellular and extracellular mechanism {McCann et al., 1994} When a water deficit occurs, the ionic concentration of the extracellular space is increased. This results in the extracellular space taking water from the intracellular space and causing cell shrinkage. This cell shrinkage is detected by receptors in the brain, and in turn a hormonal response is produced to initiate drinking. Conversely, when the body has an excess of water, the reverse process occurs. A lower ionic concentration in the extracellular fluid allows more water to transfer into the intracellular space. Cells become filled, drinking is inhibited, and the kidneys excrete more urine. The kidneys are critical in the regulation of water balance, blood pressure, filtering waste products from blood, and making urine more concentrated or more dilute. When water losses exceed water intake, the osmotic pressure of extracellular fluids is increased and antidiuretic hormone (ADH) is released. {Jequier E, 2010} Both of these events initiate a feeling of thirst. These series of events occur as blood plasma volume drops and the extracellular fluid osmotic pressure increases at water deficits that equate to a weight loss of 1-3%. These events can also activate the kidneys to increase water reabsorption before thirst is ever elicited.

Endocrine Control of Water Balance

Neuroendocrine factors regulate water balance. Short-term regulation of osmolality is controlled by neural elements, while long-term regulation is humoral or endocrine in nature. {Anderson RS, 1982} Serum sodium is responsible for most of the osmotically active particles that contribute to serum osmolarity; serum glucose and urea also contribute to serum osmolarity. Water loss increases concentrations of solutes in plasma or serum, thereby increasing serum osmolarity. Blood volume, hydration status, and ADH are intimately involved in controlling extracellular fluid volume. Low circulating blood volume stimulates carotid and aortic baroreceptors to respond to changes in blood pressure, causing ADH secretion {Ramsay et al., 1988}. Hyperosmolarity affects the osmoreceptors in the hypothalamus and stimulates ADH secretion from the neurohypophysis; the hypothalamic thirst center is also stimulated and causes an increase in water consumption to counteract serum hyperosmolarity by solute dilution. Rapid increases in serum osmolarity cause water movement along its concentration gradient from intracellular to extracellular spaces, resulting in neuronal dehydration, cell shrinkage, and cell death; cerebral vessels may weaken and hemorrhage. Vasopressin, released by the posterior pituitary, causes vasoconstriction acutely and fluid retention chronically to elevate systemic blood pressure. Therefore, blood volume and blood pressure are intimately interconnected.

Chronic Dehydration- How Are Cats Susceptible?

Cats in particular are susceptible to dehydration merely by way of their evolution as obligate carnivores. Cats do not naturally drink water when eating wet food or fresh prey, which is about 60-70% water; furthermore, cats have a reduced thirst drive even when eating a dry diet. {Prentiss PG, 1959}

The water content of commercial foods varies from approximately 8% in dry foods to 75% in wet foods. In addition, the composition of the diet is important in determining the amount of water ingested to maintain water homeostasis; cats on a dry food only diet consume approximately 100 ml of water per day whereas cats on wet food drink infrequently or not at all. {Hendriks et al. 1999}. Cats adjust their water intake to the dry matter content rather than the moisture content of the diet. {Zoran DL, 2011} When dehydrated, cats are slower to initiate drinking and take almost a day longer than dogs to replenish severe dehydration deficits. {Adolf EF, 1947} {Caldwell FT, 1931}

Cats consuming dry food do not drink enough water to be equivalent to the water contained in a wet ration with the same nutrient composition. In fact, a recent studied showed that cats fed a wet diet (70% moisture) content had lower urine specific gravity, weight gain and more physical activity than those fed a low moisture diet (10% moisture). {Deng et al., 2014} The reduced thirst response in cats has been observed; however, the relationship between

vasopressin and triggering of the thirst response has not been studied in cats. One study showed that vasopressin secretion occurs in cats when plasma osmolality approaches 310-330 mOsm/kg; {Reaves et al., 1981}; however, another study suggested that cats can exhibit plasma osmolality in the range of 330-350 mOsm/kg without increasing water consumption when fed an entirely dry diet. {Zanghi et al., 2018}

Cats have certain physical features that reduce their ability to see still water and to consume water from water bowls. (Figure 1) As a predator, a cat's eyes are designed for bipolar vision and focusing at distance. In fact, cats may have trouble focusing from near to distant objects and appear to not focus at all on objects closer than 25 cm away. {Turner DC, 2014} Therefore, cats will have a difficult time visualizing the water meniscus in a water bowl and often prefer to drink from faucets or to lick water from surfaces (such as the shower). Furthermore, cats are also inefficient at lapping low viscosity fluids, such as water. This is a result of the anatomy of the tongue and the mechanism of pulling water into the mouth. A cat will insert the tongue at 90 degrees into the water and curl the tongue backwards forming a small ladle. {Reis et al., 2010} The fluid is then pulled towards the mouth forming a small column which the cat "bites off" to deliver less than 3/100ths of a tsp of fluid into the mouth with each lap. {Reis et al., 2010} The amount of fluid consumed is also dependent on the viscosity of the fluid; milk or gravy will be more easily consumed because of higher viscosity.

Cats have also evolved to exhibit several behavioral traits that cause them to drink less than dogs. In general, cats prefer fresh, untainted, moving water and they may refuse water from containers that harbor odors or bacteria. Many cats will feel vulnerable to attack by other cats or dogs in the household while drinking water from a communal water bowl especially if the bowl is in a corner. Water fountains do not necessarily increase water consumption or hydration in cats as evidenced by a study looking at changes in urine specific gravity in cats using water fountains {Grant, 2010}. Most of the cats that used the fountains showed no change in urine specific gravity; furthermore, several cats in the study were reluctant to use water fountains because of the noise that was generated.by the fountain pump. {Grant, 2010}

Healthy adult cats presenting to first opinion veterinary clinics invariably have urine specific gravities greater than 1.035; however, the cats in this study were consuming a dry diet or mostly dry diet.{Rishniw and Bicalho, 2015} Although it was previously thought that cats were capable of higher urine concentrating ability than dogs, it is probably not the case. Mammalian kidneys differ in the ratio of cortical to juxtamedullary nephrons and urine concentrating ability has been associated with thickness of the medulla. {Schmidt-Neilson R, 1961} Aquatic species, such as the beaver, have a very thin medulla whereas a desert species, such as the gerbil, have a very thick renal medulla. {Schmidt-Neilson R, 1961} Dogs and cats have very similar medullary thickness; therefore, it is unlikely that cats have more urine concentrating ability than dogs.

Disease States Associated With Chronic Dehydration: Urolithiasis And CRD

Cats may suffer from a variety of lower urinary tract disorders (LUTD) including urolithiasis, urethral plugs and interstitial cystitis (FIC). Cats with recurrent LUTD given a canned therapeutic diet had a greater decrease in recurrence of LUTD when compared to cats fed a dry therapeutic diet (Markwell et al,1998). Under most conditions, cats eating dry food will drink more water than cats given a canned food; yet, total water intake may be greater for cats given a canned food {Seefeldt and Chapman, 1979}

Adequate hydration may have a significant effect on aging kidneys and may contribute to preservation of renal function as the cat ages. Cats may exhibit an increase in urine output as they age with elderly cats in one study showing a decrease in urine specific gravity and increased urine output without concomitant increase in thirst at about twelve years of age. {Perez-Camargo, 2004}

In humans, this chronic under hydration may be associated with hypertension and chronic renal disease from prolonged vasopressin release which causes increased glomerular pressure and mesangial proliferation. {Bouby N, 2003} In cats, chronic dehydration is a risk factor for the development of chronic kidney disease. {Greene et al., 2014} Prolonged vasopressin release can increase glomerular pressure and mesangial proliferation. {Bouby and Fernandes 2003} High water intake was associated with attenuation of renal damage in partially nephrectomized rats compared to controls consuming normal amounts of water. {Bouby 1990} Aged cats fed a wet diet supplemented with antioxidants and fatty acids showed a less rapid increase in serum markers of renal function such BUN and creatinine. {Cupp 2008}

Feline Hydration: Can We Increase Voluntary Water Intake In Cats?

Water intake can also affect urine volume and previous studies comparing water balance in cats have shown that total body water increases and urine output increases by 50% when cats switched from an all dry to an all wet diet. {Seefeldt SL, 1979} Under most conditions, cats eating dry food will drink more water than cats given a canned food; yet, total water intake may be greater for cats given a canned food.

Feeding an entirely wet diet significantly increases water consumption, total body water and urine volume compared to an entirely dry diet. {Xu, 2014} Furthermore, adding 33%r 66% canned food a dry diet had no significant effect on urine volume or lean body mass in the same cats even though water consumption did increase. (Figure 2) This suggests that the mere addition of canned food to a dry diet is inadequate to dilute the dry matter of the diet sufficiently to affect urine specific gravity and total body water in a meaningful way. In this study, the only significant differences in hydration parameters were between an all dry diet vs an all canned diet. {Xu, 2014}

A recent publication investigated water intake and urine measures in healthy cats provided free-choice access to a nutrient-enriched water with (NWP) or without (NW) added poultry flavoring offered at 3 different volumes in addition to tap water (TW).Thirty six domestic shorthair cats were studied. Control group cats (n = 4) received dry food with TW ad libitum throughout the study. Cats of the NW and NWP groups (n = 16/group) received the same food with TW only (period 1; 7 days) followed by TW and the assigned treatment ad libitum at 1X, 1.5X, and 2X the volume of TW consumed in period 1 during periods 2 (17 days), 3 (10 days), and 4 (10 days), respectively. Liquid consumption, food intake, and total water intake (from all sources) were measured; urine collected over 48 hours in each period was measured, and urine specific gravity (USG) was determined. Total water and food calorie intake were similar among groups in period 1; total water (TW) consumption by control cats did not differ during the study. Liquid consumed by drinking increased 18%, 57%, and 96% in the NWP group and15%, 25%, and 44% in the NW group in periods 2, 3, and 4, respectively, compared with that in period 1. Increased urine output and decreased USG were significantly associated with period and treatment.(Figure 3) Increasing the volumes of NW of NWP offered to healthy cats led to increased free liquid consumption and was associated with greater urine output and dilution as measured by USG. {Zanghi 2018}

In conclusion, water intake and hence hydration in the cats can be significantly influenced by increasing total dietary moisture to over 70%. Feeding an all canned diet or using nutrient-enriched water along with a dry diet will achieve the desired goal.

Figure 1. Barriers to hydration and drinking in the domestic feline.

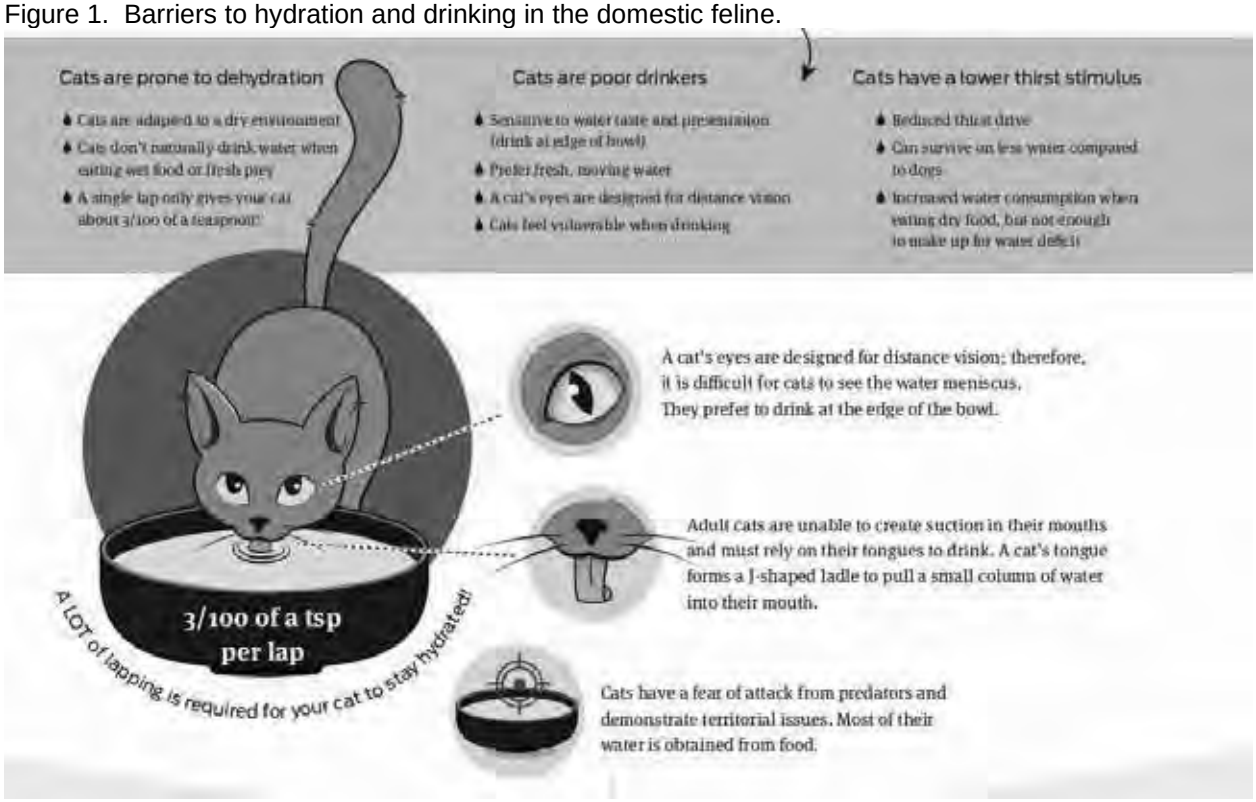


Figure 2: Total water consumption from food vs drink in cats fed inversely proportional amounts of dry vs wet food

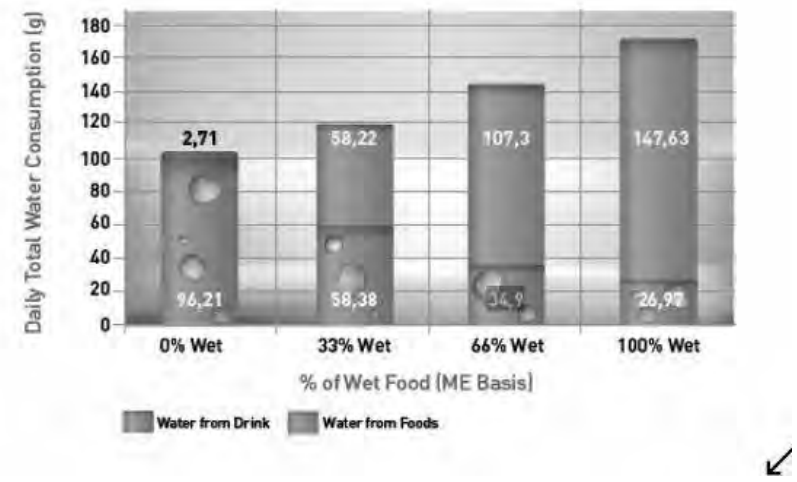
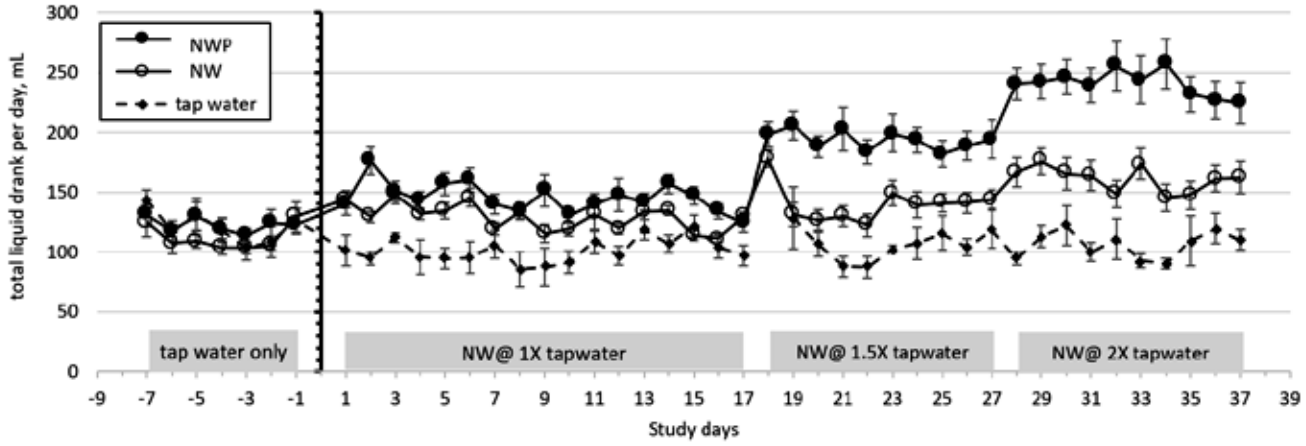


Figure 2—Mean ± SE daily amounts of free liquid consumed (by drinking) for the 36 cats in Figure 1 during periods 1 (days −7 to −1), 2 (days 1 to 17), 3 (days 18 to 27), and 4 (days 28 to 37). Black circles, white circles, and diamonds depict mean results for the NWP, NW, and control groups, respectively.



Track A

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Comorbidities: Changing the Way We Use NSAIDs

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Introduction

Nonsteroidal anti-inflammatory drugs have been used for centuries for the control of fever, pain and inflammation. Their action reflects variable inhibition of the metabolites of the cell membrane fatty acid, arachidonic acid. However, based on their mechanisms of action and thus their impact on normal physiology, their use in animals with disease increases the risk of adversity.

Role of Cyclooxygenases in Health

Mechanism of Action:

Non-selective NSAIDs target formation of prostaglandins (PGs) produced by both isoforms of cyclooxygenases (COX), 1 & 2; preferential drugs target COX 2 more than COX 1 ("preferential"; carprofen, meloxicam, deracoxib); and selective drugs minimally target COX-1 ("selective": firocoxib, robenicoxib). Dual inhibitors (tepoxalin) target both COX 1 and 2 as well as the formation of leukotrienes mediated by lipoxygenases (LOX). For all, inhibition of COX is dose and drug-dependent. Target pharmacologic effects include, in order of dose, antipyresis, analgesia, and control of inflammation. However, unintentional effects reflecting inhibition of homeostatic PGs target all tissues in the body. Simplistically, PGs influence normal physiology and might best be predicted to be protective in nature. Constitutive PGs are mediated by COX-1 and are generally measured by inhibition of platelet activity (thromboxane); they also are responsible for homeostasis in most tissues. Inducible PGs mediated by COX-2 are responsible for homeostasis or a return to homeostasis on an "as needed" basis; activity is generally measured following endotoxin stimulation of mononuclear phagocytic cells. The ratio of COX 1 to COX 2 describes the amount of drug necessary to inhibit the respective isoform of the cyclooxygenase enzyme. A COX 1 : COX 2 ratio of greater than 1 indicates that the drug is more potent toward COX-2, and as such the drug might be expected to be safer and more effective compared to a ratio of < 1. Few ratios have been determined in cats: carprofen has a ratio of 5.5 (compared to 6.5 for the dog) and robenacoxib 502. The marked differences in the ratios should not be overinterpreted because research methods are markedly variable. Further, the variable effects of PGs in the body COX-2, suggest that this *in vitro* test might best be relegated to a screening tool. Manufacture bias should be avoided. Acetaminophen deserves special address: its mechanism of action is prior to that of traditional NSAIDs, targeting intermediary metabolites. As such, its anti-inflammatory effects are more limited compared to antipyresis and analgesic effects. Grapiprant also warrants special consideration since it blocks prostaglandin (specifically EP4) receptors, which presumably increases safety; its role as a feline analgesic is to be determined.

Physiologic Effects

In general, inhibition of COX-2 is responsible for both efficacy as an anti-inflammatory and avoidance of COX-1 is responsible for safety. However, this simplistic approach may lead to therapeutic failure and increasing morbidity. Both COX-1 and COX- are constitutively expressed in many tissues and COX-1 does appear to have some role in inflammation. **Inflammation:** Clearly, PGE2 from COX-2 is a major role player in inflammation through multiple pathways and as such, is a reasonable target for control of pain and inflammation. However, some inflammation is mediate by COX-1. Further, COX-2 induction in response to inflammation may play a role in tissue healing. Impaired COX-2 formation impairs healing in ligaments, bone, the GI tract and other tissues. The importance of COX-2 to dermal healing is not yet known. Interestingly, inhibition of COX-2 also has been associated with exacerbation of inflammation in some animal models and for grapiprant specifically, it may increase inflammation associated with asthma. The use of NSAIDs for chemical control of fever should be reserved for situations in which the fever is causing illness. **Central Nervous System and Pain and more**: Both COX-1 and COX-2 are constitutively expressed in the brain and spinal cord. Constitutive COX is highly regulated by factors such as ischemia, immunomodulation, cytokines, toxins, brain damage and maturation processes. However, COX-2 is the predominant COX and its role in neuropathic pain is well established. PGs have been implicated in causing increased pain perception (allodonia) in damaged compared to normal tissues. Induced COX-2 PGE as been associated with hyperalgesia (exaggerated response to pain) in either the spinal cord (primary hyperalgesia) or at nociceptors in peripheral tissues (secondary hyperalgesis). Induction of spinal COX-2 in the dorsal horn also has been associated with central sensitization, manifested as a change in excitability threshold. NSAIDs may inhibit NMDA-receptor mediated neuronal cell death by preventing an increase in extraceullar glutamate concentrations released in response to increased PGs. Finally, COX-2 appears to be involved in the loss of glutamate induced apoptotic cell death. **Cancer** NSAIDs have been demonstrated to have anticancer effects associated with inhibited COX-2 (Warner 2004). Mechanisms by which COX-2 may facilitate cancer growth or spread include impaired apotosis, transactivation of epidermal growth factors or receptors (thus promoting colon cancer), and promotion of angiogenesis. The impact of COX-2 inhibitors has generally supported the role of COX-2 in cancer growth and spread.

Gastrointestinal
Both COX-1 and COX-2 are constitutively expressed in the GI tract. However, it is the constitutive expression of COX-1 that appears to play the predominant major role in the protection of the GI tract. Drugs which spare COX-1 while targeting COX-2 generally have been proven safer than those which target both COX isoforms. However, induction of COX-2 is important to the healing GI tract. Interestingly, in the pancreas, constitutive COX-2 expression dominates, although the clinical relevance of this is not yet known. Indeed, induction of COX-2 may be important to healing, regardless of the tissue, including healing bones. **Cardiovascular:** The role of PGs in the cardiovascular system is largely beneficial and the relationship between COX-1 and COX-2 and their respective PG endproducts exemplifies the complex "ying-yang" balances which characterizes this family of chemicals. Platelets contain thromboxane synthetase, which catalyzes the formation of thromboxane from arachidonic acid. Thrombosis reflects platelet aggregation and vasoconstriction. The formation of a thrombus is kept "in check" by the presence of prostacyclin synthase in vascular endothelial cells. This enzyme catalyzes metabolism of arachidonic acid to prostacyclin (PGI2), a vasodilatory and platelet inhibiting prostaglandin endproduct. However, whereas TXA2 is associated with COX-2, prostacyclin synthetase colocalizes with COX-1. Thus, whereas drugs which target both COX isoforms will potentially allow the balance to be maintained, drugs which preferentially target only one isoform risk disruption of the balance. Such may be the case with COX-2 selective NSAIDs. Their preferential inhibition of COX-2 may allow thrombus formation to go unchecked, increasing the risk of thromboembolic disorders. As such, caution is recommended when using COX-2 preferential drugs in cats at risk for arterial thrombosis. **Kidney:** In the kidney; both COX-1 and 2 are constitutively expressed. Both are formed in the macula densa of humans and animals, but COX-2 may have a more important role than COX-1. In (nonhuman) animals, iInhibition of COX-2 causes sodium and potassium retention in salt depleted, but not normal, animals. However, in humans, COX-2 appears to influence renal vasculature and podocytes. The role of COX in the kidney needs to be further elucidated before safety can be assumed for any NSAID; sparing COX-1 and targeting COX-2 can be expected to alter renal function. For example, kidneys do not develop in the embryos of COX-2 null knockout mice. The role of COX in the kidney differs among tissues and species.

Table 1. Selected NSAID Data for Dogs and Cats

Drug		Half-life (hr)
Aspirin	FE	27-45
	CA	8.6
Carprofen	CA	4.95 ± 1.32
	FE	20.1±16.6
Deracoxib	CA	3(5)
	FE	8
Firocoxib	CA	9.7± 0.98
	FE	7.8
Meloxicam	CA	23.7±7.1
	CA	15.1±5
Piroxicam	CA	40-50
	FE	13
Robenicoxib	FE	1.9 (0.5-1)
	CA	1-2
Tepoxalin	CA	2.0±1.2
metabolite		13.7±10.7
	FE	4.7±0.8
metabolite		3.5±0.4

Pharmacokinetics

The physiology of normal cats may contribute to adverse events to NSAIDs. Newer NSAIDs share a number of pharmacokinetic properties with older NSAIDs. The relevance of protein binding (which is ≥ 90%) is questionable except in patients with altered hepatic clearance. Some NSAIDs are substrates for P glycoprotein or other efflux pumps; the cat has been demonstrated to have unique differences in these proteins (ie, fluroquinolone induced retinal damage). Differences should be anticipated because of evolutionary diets. Most, if not all, NSAIDs are metabolized by the liver, with marked differences among the species. Cats are deficient is some (not all) glucuronyl transferases responsible for removal of parent and (particularly important for the cat, e.g, acetaminophen) potentially toxic metabolites. Easy depletion of glutathione transferase can contribute to an increased risk of toxicity. The Phase 1 metabolic make up of cats, and particularly cytochrome P450 is just being elucidated. No other species can accurately predict the feline CYP 450 make up. Gender differences have been demonstrated in two of the major enzymes (CYP3A (less) and CYP2D (more). Further, cats appear to have little CYP2E. Two other issues complicate predicting the disposition of NSAIDs: enantiomers and polymorphisms in drug metabolizing enzymes. The latter has been demonstrated to result in different efficiencies (poor to ultra-efficient) in drug metabolism and are likely to be demonstrated in cats, particularly those that evolved on the "other side of the pond" and thus on different diets. It is generally assumed that the half-life of NSAIDs is longer in cats compared to most others species, particularly the dog, but as Table 1 demontrates, this is not always true. Those drugs that the cat seemingly appears to tolerate particularly well are characterized by shorter half-lives.
Clearly, selected diseases will impact the risk of adverse reactions due to toxicity in cats. Liver disease or declining hepatic function in geriatric

animals (pediatric animals may not have quite be deficient) is likely to prolong half-life. Co-morbidities that require use of potentially hepatotoxic drug, drugs that induce or inhibit drug metabolizing enzymes, nephroactive drugs (diuretics, ACE inhibitors, AR blockers, aminoglycosides) or other drugs that inhibit prostaglandin synthesis increases the risk.

Safety

Gastrointestinal damage is the most common and serious side effect of the NSAIDs among species. Cats are likely to be more sensitive to the GI side effects of NSAIDs compared to people. ***Hemostasis:*** Traditional NSAIDs are able to impair platelet activity due to impaired prostaglandin (thromboxane) synthesis. At pharmacologic doses, aspirin selectively and irreversibly acetylates a serine residue of a platelet cyclooxgenase and, accordingly, will always have very low Cox 1: Cox2 ratios. However, newer NSAIDs inhibit prostacyclin, which acts to impair platelet aggregation, while minimally affecting thromboxane synthetase. As a result, thrombosis can occur relatively unchecked, predisposing patients to thrombosis (eg, Viox®). Unfortunately, it is unclear which of these drugs target predominantly Cox-2 in cats, decreasing confidence in use particularly in cats with aortic thromboembolism. Acetaminophen warrants special consideration: Its toxicity in cat reflects deficient glucuronidation. the drug is generally removed by glucuronidation. If insufficient, the drug is shunted back to phase I metabolism which results in the production of toxic metabolites (oxygen radicals). If sufficient, glutathione can remove these radicals before they cause tissue damage. Cat hemoglobin, which contains more sulfhydryl groups than most species, is particularly susceptible to oxidation. Treatment of acute toxicity or supplementation with n-acetylcysteine (or SAMe), a precursor to glutathione, helps protect the liver and treat methemoglobinemia. Inhibition of cytochrome P450 metabolism helps prevent the formation of toxic metabolites.

Renal:

The cat may be predisposed to nephrotoxicity (compared to the dog or human), perhaps in part because of differences in renal function. In the kidney, vasodilatory PGs are protective, assuring that medullary vasodilation and urinary output continue during states of renal arterial vasoconstriction. The loss of this protective effect becomes important in patients with compromised renal function. Newer NSAIDs do not appear any less likely to be associated with this effect than the traditional NSAIDs in humans. Package Insert Information can be useful in detecting toxicities that did not develop during the approval process, or for drugs which are not approved but noehteless are used in cats. Limited post-market clinical trials are often sponsored by drug companies and potentially biased. Among the most important sources of data is post market surveillance (Table 3). The FDA web site for adverse event reporting (www.fda.gov/cvm/) can be reviewed. Table 3 based on FDA's CVM website delineates the percent of ADE that were kidney associated in 2004 (generated by author). The table reveals that the proportion of adverse events of cats that reflect the kidneys (eg, 45% of meloxicam and 24% of carpfofen) is greater than that in dogs (9%), and is greater for meloxicam compared to carprofen. However, while the percent of renal ADE associated with meloxicam is higher in cats compared to carprofen, perhaps equally important is that the percent of renal ADE in cats for either NSAID is greater than that in dogs. Perhaps in response to their review of the data, the FDA went on to include a warning on the package insert regarding the risk of renal disease with meloxicam. Indeed, 8% of cats receiving meloxicam preoperatively developed an increase in BUN. A follow-up review (2010) of the ADE revealed that for all NSAIDs reviewed by the author, the ranking of indicators of renal damage was higher in cats compared to dogs. This suggests that cats may appear to a be predisposed to NSAID induced renal disease (not just meloxicam). However, a retrospective study by Gowan et al (2011, JVMS) in geriatric cats (approximately 13 yrs) whose disease was stage matched in 4 groups (with or without CKD and with or without meloxicam [0.015 to 0.03 mg/kg daily based on minimum effective dose]; n = 16 to 22 per group) found that the the change in creatinine during the year long study period was less in the group receiving meloxicam whether or not the patient had CKD. This study supports the potential long term safe use of meloxicam in cats, even with renal disease, as long as the dosing regimen is adjusted appropriately. An important consideration may be exposure to the kidneys. The half-life of meloxicam is 15 hrs in cats, and as such, even with a 24 hr dosing interval, the kidneys have no drug free time to recuperate from the potentially detrimental effects of NSAID. Robenacoxib has only a 1-2 hr half-life and as such, with once daily dosing, the kidneys have a long period during which they are not exposed to drug, allowing for recuperation. Indeed, the PI for Onsior®, no evidence of renal dysfunction was cited in the clinical trials. Caution is nonethless indicated in cats with high normal creatinine; renal

Table 3. Adverse events associated with meloxicam or carprofen in dogs or cats (based on 2004 FDA-CVM cumulative ADE data)

	Dog	Cat	Dog	Cat	Dog
	Carprofen	Carprofen	Meloxicam	Meloxicam	Derocoxib
Total	14826	489	1124	497	3658
Vomiting (%)	29.6	47.2	25.7	33.4	34.0
Diarrhea (%)	9.9	5.7	11.5	0.0	13.7
Anorexia (%)	26.3	31.3	20.2	45.5	22.3
Bun (%)	9.6	24.1	9.3	45.1	17.1
Creatinine (%)	0.0	22.3	0.0	46.3	14.9
Kidney failure (%)	0.0	5.7	0.0	23.3	0.0
Azotemia	0.0	0.0	0.0	26.1	0.0
Death	11.4	13.7	8.0	13.5	9.5

function should be intermittently monitored in cats. Because older animals may have less protective ability against NSAIDS, hepatoprotectants such as SAMe, n-acetylcysteine (especially for acute hepatopathy) or milk thistle should be considered.

Specific Drug Information

Robenacoxib: Robenacoxib is approved for use in companion animals outside the United States and has been recently approved for use in cats and dogs in the US. In the author's opinion, the major advantage of this drug compared to others is the short half-life, which (particularly in cats) decreases kidney NSAID exposure time. Isoform preference in studies supported by the manufacturer indicate a COX-1 to COX-2 ratio (95% inhibition) of 450 using whole blood assays in cats, indicated Cox-2 preference or selectivity. The disposition of robenacoxib in cats at 2 mg/kg intravenously has been reported, revealing an elimination half-life that is very short compared to meloxicam, also approved for use in the cat. Data from the ex vivo and pharmacokinetic studies were subsequently integrated with a model of inflammation in cats (n=10), resulting in a recommended dose 2 mg/kg dose every 12 hours. At 5 to 10 times the recommended dose (1-2 mg/kg), no significant changes occurred compared to placebo when dose for 28 days.

Table. Head to head comparison of the ranking (and % of total report*s) of adverse events reported for cats for meloxicam versus robenicoxib

	Meloxicam		Robenacoxib
Rant	2912	Rank	1161
Abnormal Rank	% Rep	Abnormal Rank	% Rep
Anorexia	42.2	Lethargy	19.7
Increased creatinine	40.6	Depression	14.8
Increased BUN	39.9	Anorexia	14.0
Vomiting	31.3	Lack of efficacy	12.7
Depression	30.5	Death by Euthanasia	10.9
Renal Failure	24.8	Vomiting	10.5
Increase phosphorus	18.2	Accidental exposure	10.5
Azotemia	16.8	Fever	9.8
Death by Euthanasia	12.8	Increased BUN	7.1
Death	12.1	Increased creatinine	6.7
Dehydration	8.9	Death	6.5
Diarrhea	6.0	Dehydration	6.2
Lethargy	5.7	Increase phosphorus	4.4
Fever	4.0	Increased ALT	3.7
Increased ALT	3.6	Hematamesis	1.2
Hematuria	3.1	Renal Failure	0.0
Accidental exposure	3.0	Azotemia	0.0
Hematamesis	1.1	Diarrhea	0.0
Melena	0.9	Hematuria	0.0

*The number reported for that adverse event was divided by the total number of adverse event reports for that drug. The rank was based on the highest proportion for that drug

From the FDA Adverse Event Reporting site for the Center for Veterinary Medicine; evaluated 7/9/2019

When dose for 44 days, creatinine increased in all groups (including placebo), with the increase being significantly different from placebo only for the 2 mg/kg (but not 6 or 10 mg/kg) group (n=8/group). The authors concluded that robenacoxib was not associated with any biologically relevant toxicity even at 20 mg/kg for 42 days. In the FOI associated with Onsior® approval, cats (n=8; 8 mos old) receiving 4 or 10 X the recommended dose for 21 days or up to 5 X the dose for 6 months remained clinically normal, but had lower kidney weights compared to placebo. The apparent safety of robenacoxib may reflect not only is potency for Cox-2, but also is short plasma elimination half-life. Its efficacy appears to benefit from a longer presence at sites of inflammation, with control of pain (and inhibition of Cox-2 in inflammatory exudate) occurring for 24 hours .Robenacoxib has performed favorably (non inferior) to ketoprofen for treatment of musculoskeletal disorders in cats. The product has not been on the market sufficient long for post market surveillance to make an impact on safety assessment.

Meloxicam

Meloxicam, like piroxicam, is a member of the oxicam group of NSAIDs The COX2:COX1 ratio for meloxicam, unlike that for piroxicam, favors selective COX2 inhibition in humans, suggesting that it has a wider margin of safety than most other. However, in cats, it is not clear if piroxicam is COX2 versus COX1-protective. Both piroxicam and meloxicam are characterized by a shorter half-life in cats compared to dogs. Meloxicam is more potent (although not necessarily more efficacious) than aspirin, indomethacin, and piroxicam; hence, its dose is smaller. The disposition of meloxicam has been studied in cats. Meloxicam is among the NSAIDs characterized by a shorter half-life in cats compared to dogs, and is one of the few NSAIDS that appear to be well tolerated in cats. It's safe use in Canada for several years predated its approval for use in cats in the US. Meloxicam is the only NSAID approved for use in cats in the United States. However, despite its apparent safety compared to other NSAIDs, the therapeutic margin of meloxicam is relatively narrow. Cats do not tolerate doses greater than or equal to 0.3 mg/kg gastric ulceration and death has occurred at 3X to 6X the normal for 10 days. Several studies support the efficacy of meloxicam in cats. In

one study, the optimal dose of meloxicam to prevent endotoxin-induced fever in cats was 0.3 mg/kg, a dose also noted for its ability to cause toxicity. Meloxicam (0.2 mg/kg SC), carprofen (4 mg/kg SC), tolfenamic acid (4 mg/kg SC) and ketoprofen (2 mg/kg SC) did not differ in their ability to control post-operative pain following OHE in cats in one study. Meloxicam has been approved in Australia for chronic use at a dose of 0.05 mg/kg daily in cats. Genuw (J Fel Med Surg 2008) recently reported the safe used of meloxicam in adult (aged) cats using a case-control design (n=46; treated cats, age 12.9$\pm$4.2 yr) in Australia. Meloxicam was administered at 0.1 mg/cat (0.01-0.03 mg/kg (0.1 mg/cat) with food once daily following a 0.1 mg/kg once daily for 4 days oral loading dose. Mean duration of treatment was 5.8 months. However, there are some issues with the study. Since it was case controlled, no placebo of blinding took place and efficacy comparisons were based on comparison at baseline. Thus, it is difficult to assess efficacy. Illnesses in both the treatment and control group were diverse, with 25% of each group suffering from some disease. Ten pairs of cats were matched by disease. Cats with renal disease were included if disease was stable. One cat in each group died due to chronic renal insufficiency. Creatinine was measured only in the first 10 pairs of cats and only until 1 month of therapy. No statistical differences were found in creatinine between the treatment and control group (data not provided) at 1 month; however, the power of the study was not reported. One cat in each group died from chronic renal insufficiency; creatinine increased in cats with pre-existing disease treated with meloxicam numerically more than it did in control cats with the exception of 6 months (data not provided to evaluate variability). In addition, 4 cats in the meloxicam group and one in the control group developed vomiting. Caution is suggested when interpreting the results of this study as evidence of safety of meloxicam in regards to renal dysfunction associated with long term therapy. Caution is thus encouraged when using any NSAID, and perhaps meloxicam, in cats with pre-existing renal disease; this may include that population of cats whose serum creatinines are “high” normal.

Others:

Piroxicam is an oxicam NSAID approved for humans.It has received attention for its ability to reduce the size of tumors (transitional cell tumors and others) in dogs. Piroxicam may interact by an additive or synergistic action with anticancer drugs to cause tumor cell death. Piroxicam is a potent antiinflammatory in musculoskeletal conditions.The disposition of piroxicam has been studied in the cat. Notably, the half-life of the drug is much shorter in cats (12 hours) compared with dogs (40 to 50 hours). Little information ir available for this drug in cats. Cox1:Cox2 ratios have not been determined. **Grapiprant:** The most recently approved drug that targets specific small molecules is the non-cox-inhibiting NSAID, grapiprant (Galliprant®). Indicated for treatment of osteoarthritis, this drug differs from nonsteroidal anti-inflammatories (which target cyclooxygenase, and newer ones, cyclooxygenase 2) by targeting (antagonizing) the prostaglandin E-2 EP4 receptor. However, importantly, targeting E4 only can disrupt the balance in the effects of PG. Further, EP4 mediates important physiologic effects and as such, caution is still indicated. Finally, other receptors play a role in inflammation. As such, efficacy of EP4 receptors needs to be demonstrated. The half-life ranges from 2 to 8 hrs, being 3 fold longer in female compared to male cats. The drug appears to be safe at least based on a 28 day study at up to 15 mg/kg. ADE reports are limited to 2 cats (both died).

NOTES:

NOTES:

Antimicrobial Risk: Changing Your Approach to Therapy When Comorbidities Exist

Dawn Boothe, DVM, MS, PhD, DACVIM, ACVCP

Antimicrobial Resistance Patterns in the Cat

The advent of antimicrobial resistance is increasingly limiting therapeutic options in human and resistance to an antimicrobial varies with the species and strain. Critical to slowing this relentless march towards inefficacy is changing our prescribing behaviors. Understanding the mechanisms where by resistance emerges, the state of resistance to day and the risk factors for therapeutic failure is paramount to improving prescribing behaviors for the cat.

Gram Negative Resistance:

Among the most adaptable organisms is E. coli. Escherichia coli, a member of the family Enterobacteriaceae, is the predominant facultative anaerobe playing a major role as normal microflora.[1-2] However, it also is ubiquitous in the environment, as is recognized by its appearance as contaminants in food stuffs. Its presence in the environment is used as a sentinel of environmental contamination. Referred to as the "cockroach" of microbes because of its adaptability, E. coli rapidly divides, potentially doubling its population every 20 minutes and it is highly mutagenic. The gastrointestinal environment is conducive to development of resistance to coliforms. Environmental microbes maintain an ecological niche by suppressing competition through secretion of antibiotics. As such, commensal organisms are constantly being exposed to antibiotics. However, the microbe producing the antibiotic, as well as surrounding normal flora, are resistant to the antibiotic. Thus, genes for resistance develop along with genes directing antibiotic production and organisms are "primed" to develop resistance. Microflora of the GI tract can serve as reservoir of resistance genes, perhaps facilitating the idea of "good" versus "bad" organisms. Exposure to antimicrobials facilitates survival of isolates that have either spontaneously mutated or acquired resistant through other means. Resistance may be easily conferred to other potentially more virulent organisms. The impact of antimicrobials on the feline gastrointestinal microflora has not been studied but if other species are an indicator, resistance to the used drugs will occur within days of treatment and what is left behind will be resistant to the drug. In dogs, enrofloxacin causes all surviving (which are many) gastrointestinal *E. coli* to express high level multidrug resistance which has not resolved by 3 weeks after dosing. Further, using metronidazole as an example, return of the microbiota to its normal healthy state may take years. The use of probiotics designed for the cat ultimately may be an appealing means to minimizing the impact of antimicrobial use (oral or parenteral). The probiotic ideally would be broad in its diversity rather than a single organism.

E. coli has developed resistance to the fluorinated quinolones, beta-lactams, or both. For beta-lactams, it is among the Gram negative organisms that secrete extended spectrum beta-lactamases (ESBL). The ESBLs are encoded by large plasmids that can confer the information between strains as well as different species of organisms. The gene mutation confers resistance to newer cephalosporins which should be considered higher tier drugs. These include cefotaxime, ceftazidime and ceftriaxone, cefpodoxime and cefovecin. However, interestingly, clavulanic acid and sulbactam may not be affected. The ESBL are most commonly found in Klebsiella spp, E. coli or Proteus mirabilis (3.1-9.5%), but they also have been detected in other members of the Enterobacteriaceae and in Pseudomonas aeruginosa. E. coli rapidly develops resistance particularly that associated with multiple drug resistance (MDR) when exposed to selected antimicrobials, particularly fluoroquinolones. Normally associated with point mutations in topoisomerases (DNA Gyrase and Topoisomerase IV), such resistance is, like beta-lactamases, within class. Increasing MIC indicate the development of resistance; most isolates with MIC of 0.125 or more, even though considered "susceptible" have already started

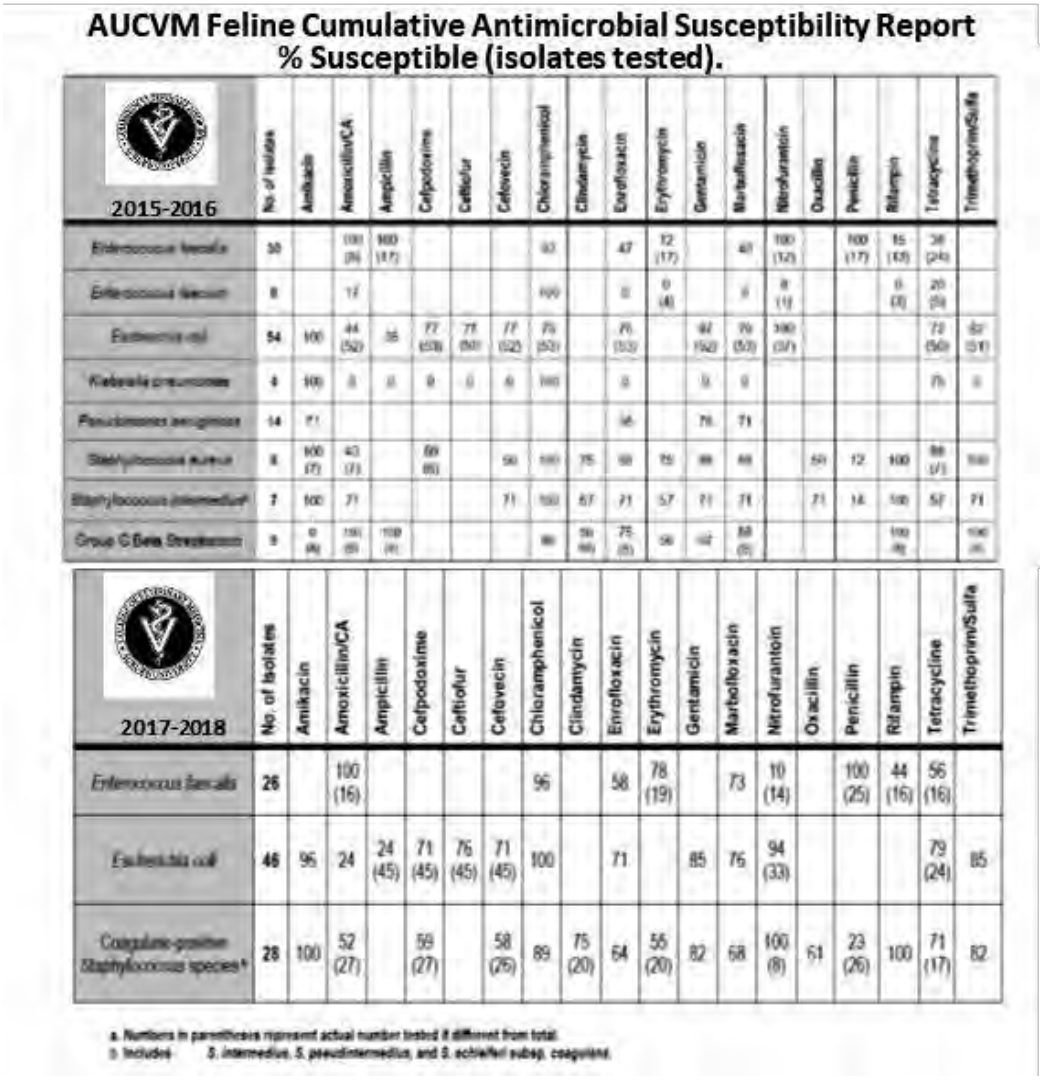
Table. Percent of *E. coli* resistant to commonly used antimicrobials

Drugs	Overall (n = 1512)	95% CI	Species	
			Canine	Feline
AMXC	41.5	39.1-44.0	45.2	30.0
AMP	49.1	46.6-51.6	52.8	37.6
CPF	9.3	7.7-11.0	10.5	5.7
CFT	8.5	7.1-9.9	9.6	4.9
CFO	12.8	11.1-14.5	14.2	8.5
CFP	13.0	11.3-14.7	13.7	10.6
CFZ	8.9	7.5-10.5	10.4	4.4
CPL	98.9	98.2-99.3	99.0	98.6
CHP	12.6	11.0-14.3	13.7	9.3
DXY	100			
ENR	10.5	8.8-12.3	11.69	6.7
GEN	7.9	6.6-9.3	8.56	6.0
MRP	1.3	0.7-2.0	1.05	1.9
TCL	19.4	17.5-21.4	20.79	15.3
TMS	8.9	7.4-10.3	9.69	6.3

developoing resistance. Disconcertingly, in the presence of continued drug, efflux pumps appear to be induced. Such pumps serve to remove toxic compounds from the organism, including antimicrobials. At least 5 efflux pump systems have been characterized; they are associated with porins. After only 10 minutes of exposure in vitro, E coli turns its pumps on, resulting in high level MDR, regardless of the host species. As such, fluoroquinones should be higher tier drugs and underdosing these concentration dependent drugs should be avoided.

Where are we today?

In a surveillance study of approximately 800 E. coli pathogens collected from cats (72% female, 28% male; most from the urine with approximately 10% of these being asymptomatic; proportion increased with age). The pattern of resistance varied regionally, being as much as 50% to amoxicillin or amoxicillin clavulanic acid and in the south, approximately 30% to enrofloxacin. Although the number of isolates resistant to beta lactams only (expressing single drug resistance) was high, single drug resistance to enrofloxacin was rare. If resistance was expressed to enrofloxacin, it was multidrug in nature. Currently, regional differences in resistance continue to persist. Overall resistance is greatest to cephalexin (9%) as is demonstrated in Table 1; 100% of isolates are also resistant to doxycycline using the new interpretive criteria established by CLSI. Further, 30% are resistant to amoxi-clavulanic acid and 38% to ampicillin (amoxicillin). However, in our hospital (a tertiary care center), the statistics are not as forgiving, with less than 40% of our isolates susceptible in 2015 and only 24% in 2018. The marked increase is sobering and is worse than that (at least in our hospital) in dogs. This latter statistic suggests that for treatment of E. coli¸ Clavamox® may not have that much advantage over amoxicillin along and this would also be true if treating Enteroccocus. However, if treating other organisms, protection against betalactamases may be helpful.



AUCVM Feline Cumulative Antimicrobial Susceptibility Report
% Susceptible (isolates tested).

2015-2016	No. of isolates	Amikacin	Amoxicillin/CA	Ampicillin	Cefpodoxime	Ceftiofur	Cefovecin	Chloramphenicol	Clindamycin	Enrofloxacin	Erythromycin	Gentamicin	Marbofloxacin	Nitrofurantoin	Oxacillin	Penicillin	Rifampin	Tetracycline	Trimethoprim/Sulfa
Enterococcus faecalis	30		(6)	(17)				93		47	12 (17)		40	100 (12)		100 (17)	15 (13)	38 (24)	
Enterococcus faecium	8		12					100		0	0 (8)		0	8 (1)			0 (0)	20 (5)	
Escherichia coli	54	100	44 (52)	35	77 (53)	71 (50)	77 (52)	75 (53)		75 (53)		82 (52)	76 (53)	100 (37)				72 (50)	62 (31)
Klebsiella pneumoniae	4	100	0	0	0	0	0	100		0		0	0					75	0
Pseudomonas aeruginosa	14	71								36		71	71						
Staphylococcus aureus	8	100 (7)	43 (3)		88 (6)		50	100	75	50	75	86	88		50	12	100	88 (7)	100
Staphylococcus pseudintermedius	7	100	71				71	100	57	71	57	71	71		71	14	100	57	71
Group G Beta Streptococcus	5	0 (4)	100 (5)	100 (4)				80	50 (40)	75 (5)	50	100	80 (5)				100 (4)		100 (4)

2017-2018	No. of Isolates	Amikacin	Amoxicillin/CA	Ampicillin	Cefpodoxime	Ceftiofur	Cefovecin	Chloramphenicol	Clindamycin	Enrofloxacin	Erythromycin	Gentamicin	Marbofloxacin	Nitrofurantoin	Oxacillin	Penicillin	Rifampin	Tetracycline	Trimethoprim/Sulfa
Enterococcus faecalis	26		100 (16)					96		58	78 (19)		73	10 (14)		100 (25)	44 (16)	56 (16)	
Escherichia coli	46	96	24	24 (45)	71 (45)	76 (45)	71 (45)	100		71		85	76	94 (33)				79 (24)	85
Coagulase-positive Staphylococcus species[b]	28	100	52 (27)		59 (27)		58 (26)	89	75 (20)	64	55 (20)	82	68	100 (8)	61	23 (26)	100	71 (17)	82

a. Numbers in parentheses represent actual number tested if different from total.
b. Includes *S. intermedius*, *S. pseudintermedius*, and *S. schleiferi* subsp. *coagulans*.

Gram Positive Organisms:

Methicillin resistance (MRSA; S. aureus; MRSP; S. intermedius [pseudintermedius]

Multidrug resistance is now considered the normal response to antibiotics for Gram positive cocci pneumococci, enterococcis and staphylococci. Methicillin resistance (MRSA; S. aureus; MRSP; S. intermedius [pseudintermedius] is indicated by the presence of the mecA gene, which encodes a mutation in penicillin binding protein (PBP) resulting in formation of PBP2a rather than PBP2. As such, affinity is reduced for the beta-lactam ring, rendering the organism resistant to all beta-lactams. Protectors such as clavulanic acid are ineffective. Detection of MRSA or MRSP on C&S generally is based on resistance to oxacillin, However, increasingly, laboratories are indicating MRS based on absence of susceptibility to any beta-lactam. **Where are we today?** In our hospital, based on our antibiogram, approximately 61% of Staphylococcus isolates express methicillin resistance: about 50% in *St.aureus* versus 30% *St. pseudintermedius*. This is better than in the dog for which the statistics are 49% *St. pseudintermedius* and 60% *St. aureus.*

These data suggest that canine antibiograms may be similar to feline antibiograms, but distinct differences do exist suggesting the culture may be important particularly in patients at risk due to co morbidities.

Reducing Resistance: The Three "D"s.
Regardless of the organism, the most significant mechanism by which bacterial resistance is likely to be reduced is implementation of judicious use prescribing behaviors. Consider the three DE-s:

(1) **DE-ESCALATE**. The Center for Disease Control indicates that use (regardless of rational or not) is the single biggest risk factor for emergent antimicrobial resistance. As such, approaches which minimize use, including indiscriminant use or duration will be important. Examples of human strategies include improving appropriate antimicrobial use include improving the basis for using drugs, setting limits on the duration of antimicrobial therapy, prior approval to verify proper use of select antimicrobials, and more rationale strategies such as narrowing the spectrum of empiric antibiotics, and rotating the use of antimicrobial drugs on a regular schedule. Probably the single most important first step in judicious antimicrobial use and avoiding resistance is questioning/confirming the need for therapy. What constitutes an infection in the urinary bladder may not depend only on the inoculum size (e.g, 1000 CFU/ml) but the presence of clinical signs. For urinary tract infections, increasingly the need for treating asymptomatic bacteria is questioned. Likewise, the routine use of antimicrobials in the presence of respiratory signs should be questioned ss is routine surgical prophylaxis. The Package Insert for Pradofloxacin indicates that while 70% of cats receiving the drug responded, so did 40% of cats that received no antimicrobial. Those 40% ers need to be identified. Feline abscesses are an easy target to de-escalate.

A narrow spectrum is ALWAYS preferred to a broad spectrum drug but using the lowest tier is preferred. Another tool to de-escalate is decreasing our duration of therapy. Recommendations are to continue therapy, in most cases, for 1 to 2 days after resolution of clinical signs. 5 to 7 days should be the target with most infections. In the case of very serious infections for which drugs are used in combination to enhance the spectrum, to target multidrug resistant organisms, using the higher tier AT AN APPROPRIATE DOSE (in combination) for 3 to 5 days and then withdrawing one and continuing only with the 2nd should be considered.

(2) DECONTAMINATE: Patient strategies can be critical to success: reducing inoculum size (fewer drug molecules are needed, less chance of shared or selectional resistance developing), reducing debris that serves as a nidus for infection and most importantly, perhaps, reducing biofilm. Hospital strategies include: improving infection control (eg, selective decontamination procedures, prevention of horizontal transmission via handwashing, use of disinfectants, glove and gown use, alternatives to soap, and improving the workload and facilities for health care workers), and identification of specific areas for treatment of potentially infectious agents (ie, bandaging areas that can be easily cleaned). Increasingly "detergent" should be applied to the patient and its home. For example, recurrent infections might be reduced if successful initial therapy is coupled with cleansing of the environment in which the pet is located such that it is not continued to be exposed to the infecting bug. For UTI infections, this may become particularly important in that urine contaminates the environment.

(3) DESIGN. Dosing regimens should be designed to assure that adequate drug concentrations are reached at the site of infection to kill, not simply inhibit, microbial growth. **DEAD BUGS DON'T MUTATE**! Once the decision to use the antimicrobial is made, efforts should focus selecting a drug to which the bug is most susceptible by comparing what is needed (MIC or MIC90) to what will be achieved with the chosen dose (eg, Cmax in plasma). Identifying the organism is going to be difficult without the benefit of a well collected culture. Gram staining the sample can be an effective method for immediate drug choice. The Target® Antimicrobial Handbook (Antech data) summarizes data throughout the US and has the advantage of identifying the organisms most commonly cultured (but NOT necessarily pathogens) from the various sites in cats, and provides susceptibility antibiograms. A practice-based antibiogram (see above) may be helpful. If an animal has not been exposed to antimicrobials, the chances are improved that any infecting pathogens are among the susceptible isolates.

Assessing risk factors in the patient is among the most critical means of assuring effective concentrations are reached in your patient. Any antimicrobial exposure (previous disease, co morbidities, or even exposure to another household member on antimicrobials) decreases the ability to predict susceptibility patterns. Understanding the pathophysiology of the disease is critical to therapeutic success. Urinary tract infections are probably among the most difficult to treat: organisms invade the uroepithelial cell, produce biofilm and become quiescent, three profoundly compounding risk failures for failure. Add this to the cat that is not concentrating its urine, and failure is easy to envision. Note that may asymptomatic organisms causing bacteria are caused by multidrug resistant bugs: they have to drop virulence genes to acquire resistance genes. If the patient becomes symptomatic (that is, infection emerges again), it si possible the resistance genes have been dropped to become virulent. Reculturing is indicated.

Table: Organisms most commonly CULTURED* from body sites in cats							
Site Rank	1st	2nd	3rd	4th	5th	Key	Organism
Abdominal Fluid	ECO	ENT	PAM	BHS	STA	BHS	Beta-hem-Strep
Bone	PAM	PSA	ECO	ENT		BBR	Bord.bronchisep
Genital	ECO	ENT	PSA			ECO	E. coli
Heptatobiliary	ECO	ENT	OAN	PSA		ENT	Enterococcus sp
Oral/Gingival	OAN	PAM	ECO			KLP	Klebs pneum
Pleural Fluid	PAM	ENT	ECO			OAN	Obligate anerobes
Pyodemra	PAM	ECO	STA	PSA		PAM	P.multicida
Respiratory, Lower	PAM	PSA	ECO	ENT	BBR	PRM	Proteus mir
Respiratory, Upper	PSA	PAM	ECO	BBR		PSA	Pse. Aeuriginosa
Urinary Tract, Lower	ECO	PMR	STP	KLP		STA	St. aureus
Wound/Abscesses	PAM	OAN	ECO	ENT	PSA	STP	St. intermedius
*From the Target Antimicrobial Handbook 5th ed. Organisms are Not necessarily pathogens and culture technique must always be suspect. Organisms ranked in order of percent							

A previously underappreciated risk factor (Boothe's opinioin) for resistance is any co-morbidity that requires drug therapy. Clearly, immunosuppressive diseases handicap the patient's ability to overcome underdosing. However, note that microbes do not mount resistance only to antimicrobials, but will do so toward any foreign compound. As such, the more drugs the patient is receiving, the greater the risk of resistance. For example, *E. coli* has been demonstrated to develop multidrug resistance in response to fluoxetine.

Bacterial Pathogen	Origin	No. of Isolates	Cefovecin MIC (µg/ml)			
			Min	Max	MIC_{50}[1]	MIC_{90}[2]
Staphylococcus intermedius	Dog	226	≤0.06	8	0.12	0.25
	Cat	44	≤0.06	8	0.12	0.25
β-haemolytic *Streptococcus* spp.	Dog	52	≤0.06	16	≤0.06	0.12
	Cat	34	≤0.06	1	≤0.06	0.12
Coagulase negative *Staphylococcus* spp.[4]	Cat	16	0.12	32	0.25	8
Staphylococcus aureus[3,4]	Dog[4]	16	0.5	1	1	1
	Cat[4]	20	0.5	>32	1	16
Coagulase positive *Staphylococcus spp.*[3,4]	Dog[4] Cat[4]	24	0.12	>32	0.25	0.5
Escherichia coli	Dog	167	0.12	>32	0.5	1
	Cat	93	0.25	8	0.5	1
Pasteurella multocida	Dog	47	≤0.06	0.12	≤0.06	0.12
	Cat	146	≤0.06	2	≤0.06	0.12
Proteus spp.	Dog	52	0.12	8	0.25	0.5
	Cat[4]	19	0.12	0.25	0.12	0.25
Enterobacter spp.[4]	Dog[4]	29	0.12	>32	1	>32
	Cat[4]	10	0.25	8	2	4
Klebsiella spp.[4]	Dog[4] Cat[4]	11	0.25	1	0.5	1
Prevotella spp.	Dog[4]	25	≤0.06	8	0.25	2
	Cat	50	≤0.06	4	0.25	0.5
Fusobacterium spp.	Cat	23	≤0.06	2	0.12	1
Bacteroides spp.	Cat	24	≤0.06	8	0.25	4

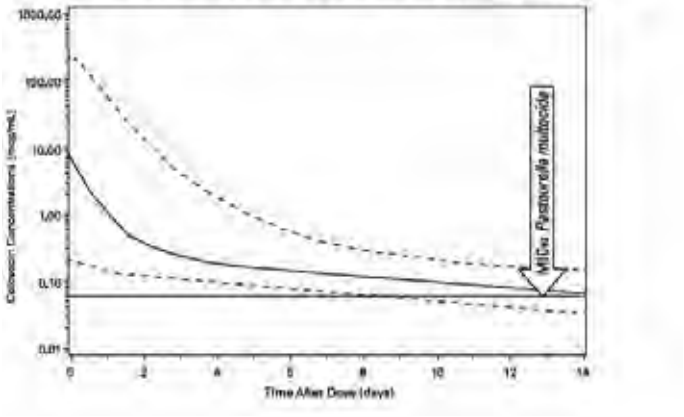
[1] Lowest concentration, which completely inhibits visible growth of at least 50% of isolates
[2] Lowest concentration, which completely inhibits visible growth of at least 90% of isolates
[3] Some of these pathogens (e.g. *S. aureus*) exhibited natural *in vitro* resistance to Cefovecin
[4] The clinical significance of these *in vitro* data has not been demonstrated.

Other considerations: One that mounts within class resistance (eg, beta-lactams) is preferred to one that promotes multidrug resistance (eg, enrofloxacin). Toxicity is a factor when considering antimicrobials. Known feline-unique toxicities to antmmicrobials are limited but include the fluoroquinolones (retinal degeneration), fosfomycin (nephrotoxicity), and potentially an increased susceptibility to chloramphenicol toxicity (decreased metabolism, but remember that this drug is a potent inhibitor of drug metabolizing enzymes in other species). Aminoglycosides (administered once daily for safety and efficacy) may be safer when administered at night for the nocturnal feline. The safety of rifampin, which will soon be the only drug we can use to treat MRS, is not known in cats. The risks of drug interactions is hard to assess in the absence of evidence.

Designing an appropriate dose is far more important than is reaching for a bactericidal rather than bacteriostatic drugs. Data regarding the disposition of antimicrobials in cats unfortunately is limited. The dog is a reasonable model in the absence of feline specific information. Some unique differences include oral bioavailability of ciprofloxacin (consider it not orally bioavailable). Water soluble drugs (beta lactams and aminoglycosides) in particular will mimic dogs. Water soluble drugs in general do a poorer job of penetrating tissues. Only 30% of amoxicillin in plasma reaches bronchial secretions, for example. Fluoroquinolones, macrolides, clindamycin and rifampin not only distribute well to tissues but accumulate in white blood cells and thus are distributed to the stie of infection.

Once the drug is chosen, design focuses on the dosing regimen to assure that concentrations adequate to kill the infecting microbe are achieved at the site of infection**.** This involves not only selecting the drug to which the isolate is most susceptible (and the drug most likely to reach the target site), but also designing the dosing regimen based on the MIC, or in the absence of patient data, then MIC 90 data. This latter data is usually not available for feline only isolates unless on package inserts (eg, fluroquinolones. Doses should be designed based on whether the drug is concentration or time dependent. Concentration dependence of fluoroquinolones should call to question the rationale use of enrofloxacin (Cmax should be 10X MIC of infecting microbe). The short half-life of time-dependent amoxicillin (1 hr) should call to question 12 hr dosing intervals. (To achieve more frequent intervals while reducing intolerance to clavulanic acid, consider administering amoxicillin alone and amoxicillin clavulanic acid in equivalent amounts: the ratio of amoxicillin/clavulanic acid increases from 4:1 to 8:1, which is close to the acceptable ratio in human amoxicillin-clavulanic acid). Remember that older package inserts had little concept of the relationships between MIC, plasma drug concentrations and efficacy, and certainly did not have the high MIC we have today. Ideally, the mutant prevention concentration would be achieved for all isolates. Finally, understand that not all susceptible isolates are equally susceptible. Refer to the cevofecin package insert MIC 90. Note that all organisms are not equally susceptible: *Pasteurella* is much more susceptible than are *E. coli* or *Staph aureus.* Compare these MIC 90s to the plot for (UNBOUD) plasma drug concentrations in cats. Note the variability in those concentrations (indicated by the 95% confidence intervals). The MIC90 for E coli is 0.5 mcg/ml: when do concentrations drop below that line in the average cat?

Figure 3: Population Predicted Free Concentration of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Cats (solid line is population prediction, dotted lines are the 5th and 95th percentiles for the population prediction).



We can use package insert for marbofloxacin in dogs and cats to demonstrate how population MIC data can be used. The MIC data for each organisms includes the MIC range, the MIC_{50} or median, and the MIC_{90}. The data for Staphylococcus pseudintermedius (135 isolates) is more robust than that of E. coli (61 isolates). The data for Staphylococcus aureus (with 12 isolates) should be applied to patients cautiously. Which organism is most susceptible to marbofloxacin? (Pasteurella because it has the lowest MIC $_{90}$). Least? (Enterococcus). The Cmax of marbofloxacin at 2.5 mg/kg is 2.0 mcg/ml and at 5 mg/kg, 4.2 mcg/ml (in the dog). The MIC 90 for St. pseudintermedius and E coli are 0.25 and 0.06 mcg/ml, respectively. E coli is more susceptible. Which dose should be used? To answer that, remember that fluoroquinolones are concentration dependent drugs, and plasma drug concentrations (or concentrations at the site) should be 10X the infecting MIC. Now which dose should be sued for which organism? (High dose would be better for St. pseudintermedius).

Table: Selected feline pharmacokinetic information for selected antimicrobials. Cmax = maximum plasma concentration of the drug at the dose (mg/kg)

Drug	**Half-Life (hr)**	**Dose (mg/kg)[1]/C_{max} (µg/mL)**
Amikacin (CD, I)	1.3±0.3	20 (IM, C)/65.6
Amoxicillin (TD, I)[67]	1-1.5	12.5 (PO)/5-6 (5.5)
Amoxicillin with clavulanic acid (TD, I)[26]	see amoxicillin	
Azithromycin (TD, S)	35	5 (PO,/0.97±0.65 (F=0.58)
Cefotaxime (TD, I) (third)	1	10 (IM)
		50 (SC,C)/30
Cefovecin (TD, I)	6.9 days	8 (SC, C)/8.5 (predicted unbound)

		8 (SC, C)/141 (bound)
Cephalexin (TD, I)	Probably 2-4	15 (PO, C)/11-29
		25 (PO, C)/15
Chloramphenicol (TD, S)	3,3 (SC)	20 (IV, C)/19.5±1.5
	6.9 (IV)	20 (PO,C)/9.8±2.6
		50 total (PO, C) 8 to 25
Ciprofloxacin (CD, I) (see also enrofloxacin)	4.53 ©	10 (IV, C)/2.53
		10 (PO, C)/0.89 (= 0.3)
Clindamycin[261,261]	16.4±15.4	2.5 (PO, C)/1.3
	7.5±1.7	5 (PO, C)/2.5
Doxycyline (TD, S)	4.6	5 (PO, C)/6
		2.5 (PO, C)/3
Enrofloxacin (CD, I)	6.7	2.5 (PO, C)/1.3
		5 (PO, C)/2.5
Florfenicol (TD, S)	4 (IV)	22 (IM, C)/20
	5.6 (IM)	22 (PO, C)/27
	7.8 (PO)	
Gentamicin (CD, I)	1.25±0.3	10 (IV/28
	1.27±0.26 (IM)	2 (IM)/4
		3 (SC)/15-17
Levofloxacin (CD, I)	8.4± 3.5	10 (IV)/5.6± 1.4
		10 (PO)/4.7± 0.9
		(F=0.86±0,44)
Marbofloxacin (CD, I)	12.7	6.2 (PO)/4.8
Orbifloxacin (CD, I)	4.5 = 5.2	2.5 (PO)/2

The International Society for Companion Animal Infectious Diseases (ISCAID) has provided *guidelines for the treatment of UTI, Respiratory Tract Infections and Skin infections of the Dog and Cat. The reader is encouraged to download these from open access sites.

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Managing Gastrointestinal Lymphoma in the Diabetic Cat
Barbara Kitchell, DVM, PhD, DACVIM (SAIM & Oncology)

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Managing Concurrent Lymphoma & Heart Disease
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Managing Renal Lymphoma in the Azotemic Cat

Barbara Kitchell, DVM, PhD, DACVIM (SAIM & Oncology)

Introduction

Among the domestic animal species, the incidence of lymphoma is relatively high in both the dog and cat. The incidence rate and disease presentation of this malignant disease in cats has changed since the advent of vaccines for the feline leukemia virus. The old literature reported rates of lymphoma in cats to be 200 cases of lymphoma or leukemia per 100,000 cats at risk per year. While definitive feline epidemiologic studies documenting the change in incidence rates of lymphoma and FeLV infection have yet to be carried out, it appears that the incidence rate of lymphoma in cats is around 20-25 cases per 100,000 cats at risk per year, which is similar to the rate seen in humans.

Lymphoma has traditionally been the most common malignancy of cats. Before vaccines for FeLV, approximately 50-70% of cats with lymphoma were FeLV positive. Recent studies of feline lymphoma patients in the 1990's suggest that only 8-14% of lymphoma cats are FeLV positive. There is also a relationship of the feline immunodeficiency virus with lymphoma in cats. The relative risks for developing leukemia/lymphoma were 5.6, 62.1, and 77.3 times greater in cats infected with FIV, FeLV, or with both infections, as compared to uninfected control cats. The average age at onset of lymphoma has been reported to be 5-6 years in cats, but this number may be misleading due to the biphasic peak in the age of incidence. Co-infected or FIV positive cats with lymphoma were significantly older than FeLV infected cats. In most recent clinical studies, the median age of lymphoma cats is 9-11 years, with the majority of cats having alimentary site lymphoma.

Classification: Lymphoma is classified based on essentially 4 criteria: histologic type, anatomic location, cytologic appearance, and immunologic type of lymphocyte affected. In many cases, the anatomic location and cytologic appearance are used to establish the working diagnosis for treating cats affected with this disease. Cytologically, tumors are classified as stem cell, lymphoblastic, prolymphocytic, histiocytic and lymphohistiocytic. Anatomic locations of this disorder in cats include alimentary, anterior mediastinal, multicentric, leukemic, and miscellaneous types (renal, ocular, neurologic, dermatologic, nasal, and various other less commonly seen locations).

Clinical Presentation

Signalment and History

There is no apparent breed or gender predisposition in feline renal lymphoma cases.
Cats with renal lymphoma typically present with clinical signs consistent with renal insufficiency. Since cats diagnosed with renal lymphoma tend to be middle-aged to older (mean age 9 years in one study), one issue for the cat that presents with azotemia is to determine whether the clinical condition represents chronic renal disease versus an acute kidney injury. In a recent study from the UK, cats with renal lymphoma had a median duration of clinical signs of only 14 days. Signs include anorexia in 50% of cats, weight loss in 42%, polydipsia and polyuria in 29%, and lethargy. On physical examination the kidneys are often large (60% of cats), sometimes extremely so, and may be smooth and diffusely infiltrated or may have nodular lymphoma areas within the parenchyma, meaning the kidneys feel “bumpy”. In a large series of cats with renal lymphoma, 84 were FeLV positive and 82 were FeLV negative but 522 cats were untested.

Etiology

Feline renal lymphomas tend to be of intermediate or high-grade subtype and are not found to be associated with retroviral infection in cats. They are believed to be spontaneously arising tumors. Environment predisposing factors may include exposure to toxic chemicals such as second-hand cigarette smoke and environmental pollutants.

Concurrent Conditions

There are no known co-morbidities associated with the diagnosis of renal lymphomas in cats. Illnesses associated with renal insufficiency can be noted, such as vomiting from hyperuricemia, but overall this tends to be an individual disease process. Because it can be extremely acute in onset, often there is no weight loss or other signs of chronic illness.

Renal lymphoma does have the unfortunate propensity to involve the central nervous system. There are shared lymphatic vessels between the renal retroperitoneal location and the thoracolumbar spinal canal, which can serve as a convenient pathway for local extension of disease. Back pain or rear limb ataxia/paresis are clinical signs that the renal lymphoma has entered the spinal canal.

Differential Diagnosis
Whenever one encounters cats that have enlarged kidneys, the primary benign differentials are perinephric cyst and potentially pyelonephritis which can cause kidney swelling. Other malignant causes of renomegaly include renal cell carcinoma or metastatic tumors affecting the kidney.

Diagnostic Examination
History of duration of illness and clinical signs are required. The minimum data base of CBC, serum chemistry and urinalysis are vital to determine the cat's overall health and renal status. Ultrasound examination is key to the diagnosis, along with fine needle aspiration cytology. Blood pressure measurements are also important, as is understanding the status of the cat's heart through radiographs and potentially echocardiogram.

Biopsy Findings
I generally perform cytopathology on renal lymphoma patients using ultrasound guidance to avoid vessels. Lymphoblasts in renal lymphoma are generally of intermediate to large size. Mitotic figures have been reported to be widely variable in number between cats, ranging from 2/10 high power fields to 40/10 high power fields. The higher mitotic index cases tended to be associated with retroviral infection. Renal epithelial cells may also be seen and are characterized by a round nucleus with somewhat granular cytoplasm. These cells are often basophilic.

Management
Cats with renal lymphoma can be among the longest lived of all feline lymphoma patients, but their initial management is critical. Cats with renal lymphoma present a true therapeutic challenge because the longer their kidneys are enlarged, the more nephron loss these cats suffer. In a way, renal lymphoma presents as truly emergent cases, because preserving renal function is time dependent. One might think of renal lymphoma as being similar to a "compartment syndrome". The renal capsule cannot stretch fast enough to accommodate a rapidly proliferating tumor burden, resulting in compression of nephron units and subsequent vascular compromise. Azotemia in cats with renal lymphoma is generally associated with a poor clinical prognosis, but these cats can be rescued with appropriate antineoplastic and fluid therapy.

I generally institute IV dexamethasone (0.2 mg/kg IV) as soon as the diagnosis is established and initiate aggressive fluid diuresis. Because azotemic cats are compromised in their ability to excrete chemotherapy renally, I generally start therapy with L-asparaginase (400IU/kg subcutaneously or intramuscularly) and vincristine (0.5 mg/m2 IV). Dexamethasone is repeated BID during hospitalization stay and the chemotherapy agents are administered once weekly for the first 2 weeks. It generally takes at least a week to see significant improvement in renal function in these cats. They often have significant diuresis, akin to post-obstructive diuresis at the renal level and thus monitoring "ins and outs" may be necessary. We generally use NoSorb beads in the litterbox so we can measure, or at least estimate ongoing renal losses to guide fluid replacement therapy. We monitor serum chemistries daily to every other day during the acute phase of illness.

Once the renal values have settled to a baseline value, we can initiate therapy with drugs that have a larger proportion of renal metabolism/excretion. The alkylating agents such as cyclophosphamide, lomustine, and chlorambucil are almost completely renally excreted. The impact of any cytotoxic drug ascribes to both the dose administered and the duration of retention in the body. Thus, prolonged retention due to lack of excretion is virtually the same as an overdose. For this reason, we avoid alkylating agents until renal function is restored.

Ultimately, the patients I have treated that have the best outcome are those that respond quickly but they often require diuresis over a number of days in the hospital. We treat with a CHOP protocol as long as renal function is normal. We always use the low end of the dose range of any drug for these cats, and are particularly careful with doxorubicin. Our normal doxorubicin dose is 1 mg/kg, but for medically frail cats I often perform a dose decrease to 0.8 mg/kg for the first dose, which is given at Week 4 of the CHOP protocol, to avoid potential renal damage.

The Modified Feline CHOP protocol that we use for cats with renal lymphoma is as follows:

Week 1: Dexamethasone 0.2 mg/kg BID tapering to SID
L-asparaginase 400 IU/KG subcutaneously or intramuscularly
Vincristine 0.5 mg/m2 IV
Aggressive fluid and electrolyte support
Monitor BUN, Creatinine and electrolytes daily initially then every other day as azotemia resolves, until discharge from the hospital.

Week 2: Prednisolone 5 mg BID PO
L-asparaginase 400 IU/KG subcutaneously or intramuscularly

Vincristine 0.5 mg/m2 IV
CBC, Serum Chemistry profile with electrolytes

Week 3: (Provided azotemia has resolved or is stably reduced)
Prednisolone 5 mg BID
Cyclophosphamide 200 mg/m2 PO
CBC, Serum Chemistry profile before administration of cyclophosphamide with dose reduction if azotemia persists

Week 4: Prednisolone 5 mg SID or BID PO, depending on cat's appetite
Vincristine 0.5 mg/kg IV
CBC

Week 5: Prednisolone 5 mg SID PO
Cyclophosphamide 200 mg/m2 PO
CBC, Serum Chemistry profile before administration of cyclophosphamide with dose reduction if azotemia persists

Week 6: Provided the cat is doing well:
Prednisolone 5 mg SID
Doxorubicin 0.8 – 1 mg/kg IV slow infusion (30 minutes) with care taken for IV catheter placement
CBC, Serum Chemistry profile before administration of doxorubicin with dose reduction if azotemia persists

Week 7: Rest week. Prednisolone 5 mg every other day

After the initial 6 weeks of therapy, we can usually proceed with an additional 3 cycles of CHOP on the standard 4 week cycle:

Week 1: CBC, vincristine 0.5 mg/m2 IV
Week 2: CBC, serum chemistry, cyclophosphamide 200 mg/m2 PO
Week 3: CBC, vincristine 0.5 mg/m2 IV
Week 4: CBC, serum chemistry, doxorubicin 0.8-1.0 mg/kg slow IV infusion (30 minutes)
Week 5: CBC, rest week

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High Grade GI Tumor with Intestinal Perforation, Spectacular Dysbiosis, & Small Cell Lymphoma

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Introduction

Among the domestic animal species, the incidence of lymphoma is relatively high in both the dog and cat. Lymphoma is a clonal expansion of neoplastic lymphocytes. The incidence rate and disease presentation of this malignant disease in cats has changed since the advent of vaccines for the feline leukemia virus. In most recent clinical studies, the median age of lymphoma cats is 9-11 years, with the majority of cats having alimentary site lymphoma. Feline alimentary lymphomas have several subtypes, including low, intermediate, and high grade lymphomas. Cell size is also used as a classifier, with small and large cell lymphomas described on histopathology reports. Most alimentary lymphomas in cats are of T cell origin and are classified by the World Health Organization scheme of Enteropathy-Associated T cell Lymphoma (EATL) type 1 and 2. The EATL type 2 form is most commonly seen in cats and is a low grade, small cell lymphoma of T cell type that are of mucosal origin. EATL type 1 lymphomas are less common and are comprised of high grade lymphomas that can be either of large or small cell type. EATL type 1 lymphomas are transmural and may be high grade. Large granular lymphocyte lymphomas are also associated with this classification. The EATL type 2 lymphomas comprise 60-75% of all feline alimentary lymphomas.

Clinical Presentation

Signalment and History

There is no apparent breed or gender predisposition in feline alimentary lymphoma cases, although some studies cite a male predisposition. Domestic shorthair and Siamese cats are overrepresented in some studies. Low grade EATL type 2 lymphomas affect older cats with a median age of 11-13 years reported.

Etiology

Viral infections: Feline leukemia virus infection is not associated with EATL in cats, as most alimentary lymphoma patients are FeLV antigen negative on blood tests and only 3% of histology specimens tested by immunohistochemistry. FeLV proviral sequences have been detected on approximately 66% of EATL type 2 tumors, which may represent endogenous viral elements or replication incompetent forms of viral infection. This finding has not been universally discovered however. FIV infection is associated with immune dysregulation and may increase the risk of developing EATL. FIV elements were discovered in the alimentary lymphoma tissues of 7 of 8 cats concurrently diagnosed with FIV infection and EATL.

Another virus that has been implicated in EATL is the panlymphotropic Gammaherpesvirus 1 in cats. This virus has been described as affecting approximately 25% of cats. This class of viruses is associated with cancer causation in humans (Epstein-Barr and Kaposi's sarcoma-associated viruses) but its role in feline lymphoma is less clear.

Bacterial infections: Bacterial infections such as *Helicobacter pylori* is associated with the development of gastric cancer in humans and in feline gastric cancers. One study noted *Helicobacter heilmannii* strains were associated with gastric lymphoma in cats in one study, but this organism has not been discovered in low grade gastrointestinal lymphomas in another study. It is unclear whether the bacteria are associated with the development of alimentary lymphoma or merely opportunistically colonize damaged mucosa. Further research is required to better understand this association.

Chronic inflammation: Concurrent inflammatory bowel disease (IBD) has been noted in up to 60% of feline alimentary lymphoma cases. It is suggested that the chronic inflammation of IBD may be predisposing to the emergence of a clonal population of T cells and therefore EATL. Cats with low grade gastrointestinal lymphoma have been found to have higher levels of COX2 and MDR1 gene expression, both inflammatory associated molecules, in cats with low grade alimentary lymphoma than in cats with IBD.

Environmental factors: There is an epidemiologic association with chronic passive cigarette smoke exposure and the development of EATL. Dietary factors have been implicated, but no clear evidence has been provided as to what component of the feline diet is most likely involved. Further studies are required to better elucidate whether diet plays a role.

Concurrent Conditions
There are no known co-morbidities associated with the diagnosis of low or high grade alimentary lymphomas in cats. Illnesses associated with advanced age are often noted in these cats, including hyperthyroidism, renal insufficiency, heart disease, and dental issues.

Differential Diagnosis
Chronic inflammatory bowel disease is a prominent differential diagnosis and may be concurrent with alimentary lymphoma in cats. Because low grade alimentary lymphoma is insidious in onset and associated with gastrointestinal signs and weight loss, a thorough evaluation for concurrent conditions should be performed. High grade gastrointestinal lymphomas in cats often present with signs of complete or partial gastrointestinal obstruction, so foreign body ingestion and other cancer types should be ruled out. Metabolic causes of vomiting and diarrhea should also be excluded.

Diagnostic Examination
History of duration of illness and clinical signs (vomiting, diarrhea, anorexia and weight loss) are required. Travel and lifestyle history may be helpful, as fungal infections with diseases like histoplasmosis may mimic signs of GI lymphoma. Diet history is generally not informative, as no specific dietary associated has been identified. Consumption of raw diets may be associated with dysbiosis and colonization with enteric pathogens.

Physical examination usually reveals a debilitated, thin patient and either intestinal masses, nodes or diffusely thickened small intestines are generally palpable. The minimum data base of CBC, serum chemistry, urinalysis, fecal testing to exclude intestinal parasites, and FeLV/FIV testing are vital to determine the cat's overall health status.

Ultrasound examination is key to the diagnosis, along with fine needle aspiration cytology or biopsy. Ultrasound reveals thickened intestinal walls and loss of layering which indicates infiltration of the muscularis layer. Measurements of the muscularis and submucosal width are used to calculate a ratio, with greater than or equal to 0.5 considered abnormal. This is not precisely diagnostic, although cats with EATL type 2 are more likely to have a thickened muscularis layer than are cases of IBD. Enlarged mesenteric lymph nodes are often noted in cats with infiltrative intestinal diseases and can be used for FNA sampling. In the case of high grade, transmural alimentary lymphoma in cats, cytology may be diagnostic of lymphoblastic lymphoma from the mass effect or from intra-abdominal lymph nodes. Small cell low grade GI lymphoma is difficult to differentiate from reactive conditions such as IBD by cytology alone, although the presence of plasma cells, eosinophils and other inflammatory cells is more likely in IBD cases.

Surgical resection with biopsy of obstructive masses is important for both diagnosis and therapy. Treatment of high grade lymphomas with chemotherapy may result in intestinal perforation as these tumors may respond rapidly to chemotherapy and even single agent prednisolone therapy so intestinal wall may be denuded. Endoscopic biopsies of the stomach, duodenum, ileum and colon may be sufficient for the diagnosis when coupled with clonality testing (PCR for Antigen Receptor Rearrangement, or PARR). Histopathology alone may not be sufficient to distinguish between IBD and EATL because features may overlap, so advanced molecular diagnostics are recommended for these cases. EATL is more associated with the jejunum and ileum while IBD is more frequently noted in the duodenum and ileum.

Biomarker testing: Many avenues of non-invasive diagnostic testing have been explored to help differentiate EATL from IBD. Hypocobalaminemia and low folate levels have been seen in both disease processes and must be corrected by vitamin B supplementation to facilitate patient recovery. Hypoalbuminemia is noted in 70% of cats with alimentary infiltrative disease, but IBD is more likely associated (77% vs. 49% in EATL type 2). This may be due to better mucosal integrity in non-inflammatory infiltrative disease. Relatively low levels of taurine have been reported in cats with colonic disease and may be associated with either malassimilation of this essential amino acid or through bacterial consumption in dysbiosis. Serum LDH levels were not noted to discriminate between cats with IBD and low grade intestinal lymphoma in one study. A thymidine kinase test was commercialized for diagnosis of feline intestinal lymphoma, but its sensitivity and specificity were only 55% and 60%, respectively, so TK testing is not a reliable differentiator of IBD vs. EATL type 2 in cats with clinical signs associated with either disease.

Biopsy Findings
Histological examination of the small intestine, jejunum, ileum and colon are definitive for diagnosis of intestinal neoplasia, although immunohistochemistry or PARR testing may be required to differentiate certain cases of IBD from EATL type 2. Guidelines have been established by the World Small Animal Veterinary Association Gastrointestinal Standardization Group for assessing feline intestinal biopsy specimens. Infiltrates into the mucosal epithelium (epitheliotropism) as well as the lamina propria of the villus, submucosa and muscularis layers may be noted in IBD as well as EATL, but intraepithelial accumulation of T lymphocytes is more likely in the villus rather than

the crypt epithelium. Intraepithelial nests of lymphocytes (5 or more small T lymphocytes) clustered within the villous epithelium are characteristic but not pathognomonic for EATL. Immunohistochemical staining with CD3 for T cells and CD 20 for B cells are most commonly employed to differentiate phenotype, although some malignancies my express both markers simultaneously. PARR testing is therefore very helpful to understanding whether the lymphocyte population is clonal as in lymphoma, or polyclonal as seen in IBD.

Management

Surgery: Surgery is both diagnostic and therapeutic in cases with obstructive mass lesions of the intestine. Obstruction is most often associated with high grade disease. Risks of surgical resection and anastomosis of intestinal lymphomas include dehiscence which typically occurs 2 to 5 days after surgery. This risk must be considered during anastomosis closure and wide surgical margins around the mass are recommended to avoid anastomosing diseased tissue. Surgical resection of the obstructive mass is highly recommended before start of dose intense chemotherapy with agents such as those in the CHOP protocol. Full thickness surgical biopsy is very helpful in diagnosis of diffuse small cell low grade lymphomas as more tissue for testing is obtained than what is typical for endoscopic biopsy. However, because small cell low grade EATL type 2 lymphomas are diffuse throughout the intestine, surgery is not therapeutic for these cases.

Chemotherapy: Chemotherapy is indicated for both low and high grade intestinal lymphomas. A CHOP or COP protocol are recommended for high grade lymphomas after surgical resection of masses. Krick et al have noted that gastrointestinal signs may be less troublesome when vinblastine is substituted for vincristine in the COP or CHOP protocol with no impact on duration of disease control.

Small cell low grade lymphomas are considered associated with prolonged lymphocyte survival rather than excessive lymphocyte proliferation, so chemotherapy agents that are targeted toward cells that are rapidly replicating are not as helpful for low grade disease. The current standard of care protocol for cats with EATL type 2 is a combination of a glucocorticoid (prednisolone, dexamethasone, or in some specific cases oral budesonide) with a modest dose of the oral alkylating agent chlorambucil. The protocol I use is daily to alternate day prednisolone, starting at 5 mg/cat twice daily for 2 weeks, tapering to SID and ultimately maintenance therapy every other day for long term care. This is combined with oral chlorambucil at a dose of 2 mg per cat PO either twice weekly, or alternate day for very large cats. I ask clients to mark a calendar to ensure alternate day dosing of chlorambucil with prednisolone. There is no significant toxicity risk if 2 mg chlorambucil is accidentally dosed twice or on consecutive days. Elderly and debilitated cats may be better served by once weekly chlorambucil dosing. This protocol is associated with remission durations ranging from over 700 to over 1100 days. No definitive endpoint to administration of these drugs has been established, as it is presumed that these cats are not cured and the protocol is non-toxic. For cats that are difficult to medicate orally at home, chlorambucil at a dose of 20 mg/m2 PO every 14-21 days has been equally successful. However, accidental double dosing of chlorambucil is associated with neurologic toxicity, manifested as myoclonus that persists for up to 3 weeks after the accident. Similarly, we may substitute triamcinolone 0.2 mg/kg by SQ injection every 14 days for cats that are difficult to pill. Very rarely do we need to risk induction of diabetes mellitus by use of methylprednisolone acetate (Depo-Medrol), but may chance it in cases of financial limitation or owner desire for palliative care only. Budesonide is administered to diabetic cats or cats with known heart disease, in the hopes that systemic exposure will be minimized through use of this poorly absorbed corticosteroid. We generally prescribe a compounded version at a dose of 1 mg PO per cat daily. However, cats with severe intestinal disease may still have some systemic exposure through their GI tract so careful observation of co-morbid cats is required. Also, this drug is extracted by first pass liver conjugation, so cats with severe liver disease may experience a higher systemic steroid exposure.

Rescue protocols: Most cats with low grade GI lymphoma do not relapse or progress to high grade disease. For cats that seem refractory to therapy, we have used cyclophosphamide 200 mg/M2 PO on days 1 and 3 every 2 weeks. Lomustine at a dose of 10m mg/cat PO every 21-28 days has been helpful as well. Finally, we have had success with intestinal radiation of cats, where a low dose of radiation applied to the abdomen has been noted to prolong survival in the rescue setting for up to 6 additional months.

Adjuvant therapy: Cats that have malassimilation syndromes, whether from IBD or gastrointestinal lymphoma, are cobalamin depleted and cannot recover well without repletion. We generally administer vitamin B12 by subcutaneous injection 250 microgram/cat once weekly for 6 weeks, then once monthly. This is logical to administer over the oral formulation, especially at the outset of disease, where malassimilation and bacterial overgrowth limits intestinal absorption.

Appetite support may be necessary despite the boost that corticosteroids give to anorexic cats. We generally start with mirtazapine 3.75 mg/cat PO every 72 hours, and if that is not helpful we administer capromorelin at a dose of 1 mg/cat PO daily.

Diet modifications may be necessary, but cats are notoriously fickle about their dietary habits. I generally attempt to use a highly palatable canned food and I am agnostic as to manufacturer since the cat decides what the cat will eat. For me, ingestion of food supersedes any theoretical consideration of the best diet. Similarly, I feel that the use of metronidazole for chronic diarrhea is helpful initially as most of these cats have altered intestinal microbiota. However, supplementation with a probiotic may also be helpful to re-establish healthy flora. Research into the best probiotic and prebiotic products available is not yet definitive and is a field that is market-driven by manufacturers. More randomized controlled studies are required to formulate appropriate recommendations.

Prognosis

Cats with small cell, low grade GI lymphoma can live out their natural life expectancy despite the diagnosis, and survivals beyond 2 years are common. Cats should be monitored monthly initially, then every other or every third month for the duration of their management. Monitoring includes a complete blood count, as bone marrow fatigue may be noted in cats that are on long-term chlorambucil therapy. Neutropenia, thrombocytopenia, and anemia may be seen and indicate a need to discontinue alkylating agent therapy. Cats that have successful surgical resection of solitary focal large cell lymphomas are among the longest-lived lymphoma patients in cats. However, cats with advanced stage of disease, including intra-abdominal node and visceral organ involved cases, have a poorer prognosis for survival with median survival expectation of 6-9 months. Causes of death include refractory relapse, comorbidities (renal, cardiac, endocrine), advanced age and end of natural life expectancy) or euthanasia based on owner's request due to clinical signs and perceived morbidity.

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Hepatic Lipidosis

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Introduction
Hepatic lipidosis is a well-recognized disease syndrome in cats. The disease may be idiopathic or develop secondary to some other underlying medical problem. Many affected cats were formerly obese and significant weight loss of up to 25% body weight may occur by the time they are presented for complaints of anorexia and weight loss. Hepatic lipidosis is the most common hepatobiliary disorder affecting cats in our hospital, as well as that reported in other hospitals in the United States. (1, 2, 3)

The liver is responsible for a variety of important functions within the body, including metabolism of carbohydrates and fats, synthesis of proteins and vitamins, storage of vitamins and iron, production of coagulation factors and removal and excretion of toxins. (4) Because the liver is involved in many crucial biological functions, a cat with liver disease may show a wide variety of signs including lethargy, anorexia, weight loss, weakness, jaundice, vomiting, diarrhea and behavioral changes.

Causes
Hepatic lipidosis is just one of the many liver diseases that can cause the signs listed above. Factors that may be associated with the onset of hepatic lipidosis include:

- Stress
- Obesity
- Anorexia
- Cancer
- Changes in the diet
- Nutritional deficiencies
- Diabetes mellitus
- Hyperthyroidism
- Any other disease that affects the cat's ability to eat

Anorexia, severe energy and protein restriction or rapid weight reduction in obese cats, however, may lead to hepatic lipidosis. (1, 2)

Anorexia will cause mobilization of free fatty acids from the adipose tissue. Free fatty acids are taken up by the liver and converted to ketone bodies or triglycerides. Triglycerides are converted to lipoproteins. Ketone bodies and lipoproteins are used by the brain and muscle for 95% of their energy requirements during absolute starvation. (2, 5, 6)

Healthy obese cats have excessive hepatic lipid accumulation because the normal liver has the ability to extract fatty acids and convert them into triglycerides at a rate greater than that required for their use in energy or lipoprotein dispersal. (2, 6) Since obese cats have the underlying tendency favoring hepatic lipid accumulation, starvation will exacerbate hepatic triglyceride accumulation due to the release of large amounts of fatty acids from the adipose stores during periods of rapid weight loss. Reduced availability of lipotrophic proteins, amino acids and other nutrients during periods of marginal food intake or anorexia will further limit lipoprotein synthesis and promote hepatic lipid accumulation. This excessive accumulation of triglycerides in the liver eventually interferes with hepatic function and liver failure results. (2, 3)

In situations of less than absolute starvation (marginal food intake), adaptation to fatty acid metabolism is also lost and excessive hepatic triglyceride accumulation results. (5, 6) This is important because ingestion or intravenous administration of dextrose or force-feeding of some diets with insufficient calories will worsen hepatic triglyceride storage. Feeding a balanced diet with sufficient caloric and protein content is essential to facilitate recovery from hepatic lipidosis syndrome.

The disease is characterized by extensive vacuolation of hepatocytes. In healthy cats, ~5% of the liver tissue contains lipids; however, in cats with hepatic lipidosis greater than 50% of the liver tissue contains lipids. This lipid is stored as vacuoles in the liver tissue. Lipid vacuolation of more than 50% is consistent with feline hepatic lipidosis syndrome. (3)

Diagnosis
Definitive diagnosis of hepatic lipidosis requires examination of either aspirates or biopsy of the liver. With hepatic lipidosis the liver will be hyperechoic on ultrasound, with respect to the falciform fat and the kidney. (2,3) A normal liver would be isoechoic to the kidney (the same echogenicity) and hypoechoic to the surrounding fat. Tentative diagnosis may be made on abdominal ultrasound by the finding of a diffuse hyperechoic hepatopathy. On blood studies, there are biochemical changes that are consistent with hepatic lipidosis. The SAP (serum alkaline phosphatase), ALT and AST will be elevated with the GGT normal to low. The history usually discloses a cat that has been either totally or partially anorexic over a period of days to weeks and as a result has undergone a sudden weight loss. The disease typically affects middle ages cats, but ranges from 0.5 to 15 years. There is no breed predisposition for this disease. (2, 3)

Fine needle aspiration of the liver is performed for cytologic evaluation. This can be done without anesthesia if the cat will remain still during the procedure. Ultrasound guided biopsy is performed if the cat is fractious, mobile or there are any questions as to whether hepatic lipidosis is the primary problem. Ultrasound guided biopsy does require general anesthesia.

The cytology or biopsy result for hepatic lipidosis shows highly vacuolated cytoplasm consistent with lipid accumulation, resulting in vacuolar hepatopathy. The pathologist should grade the lipidosis as mild, moderate, marked or severe. This will be one of the best prognostic indicators for the recovery of the cat. The more severe the changes, the poorer the prognosis. (2, 3, 4)

Treatment
Regardless of the cause, the basic treatment is the same. Many cats will be dehydrated and completely anorexic when brought into the hospital. Intravenous fluids are used to correct the dehydration. Normal nutrition must be restored to reverse the disease. (1, 4, 7) Because most cats refuse to eat, it is often necessary to place a feeding tube in order to provide adequate nutritional support. Once feeding has been restarted the cat will shift from catabolic metabolism to anabolic metabolism, in doing this they will also shift from using protein as the preferred energy source to using carbohydrates and fats. (2, 3) By providing adequate nutrition, the liver will be allowed to regain its normal function. A veterinary recovery diet is typically fed through the feeding tube for the entire time it takes the cat to recover from hepatic lipidosis-typically 8-16 weeks. Generally, these cats require 7-10 days of hospitalization to allow the food to be slowly increased until they are receiving their calculated daily kilocalorie requirements per day. The slow increase in food is necessary due to villus atrophy and ileus in the GI tract. Nausea is often seen secondary to reintroduction of food. This can be due to the GI changes or may be secondary to the liver disease. The faster the food is given, the worse the nausea can be.

When they are receiving 100% RER of food divided into three equal feedings, they can be discharged from the hospital to the care of their owners. As the liver function recovers, the appetite will gradually improve and the cats will begin to eat a regular diet on their own. The degree of recovery is related to and measured by the increase in appetite. When the cat is consistently eating normal amounts of food, without supplemental tube feeding and without weight loss, the tube can be removed. I like to want 2 weeks after the cat is totally self-feeding before removing the tube- I don't trust cats!

Feeding tubes used can include NG/NE tubes, esophagostomy tubes, and gastrostomy tubes. NE/Ng tubes are not appropriate for long term use, and cannot be used by clients at home. Esophagostomy tubes allow a wide variety of diet choices, do not require any special equipment for placement. An advantage of an endoscopically placed PEG tube is the ability to find gastric foreign bodies that would have been missed using the blind technique of placement. Additionally, if gastrointestinal disease is found during the PEG tube placement, biopsy specimens of the stomach and duodenum can also be taken at the same time.

Feeding
Once a food has been selected and the feeding amounts calculated feedings can begin. It is important to institute feeding slowly. Many of these cats have been totally or partially anorexic for some time, many metabolic changes have taken place to accommodate a starvation situation. There may be significant reductions in:

- cardiac output
- hemoglobin level and therefore oxygen carrying capacity
- renal concentration capacity
- gastrointestinal villous atrophy
- slowing of GI motility. (1, 2, 4)

Keeping in mind the changes the body has undergone while in starvation, when reintroducing food several areas need to be monitored closely to prevent the “Refeeding Syndrome”. During recovery, excessively rapid refeeding (or hyperalimentation) can overwhelm the patients already limited functional reserves. (2, 4)

Refeeding causes a shift in the body from a catabolic state where protein is the primary energy source to an anabolic state where carbohydrates are the preferred energy source. Administration of enteral or parenteral nutrition stimulates the release of insulin; this causes dramatic shifts in serum electrolytes from the extracellular space to the intracellular space, primarily phosphorus, potassium and to a lesser degree magnesium. Insulin promotes intracellular uptake of glucose and phosphorus for glycolysis.

Feedings can begin within 12 hours of PEG tube placement; this allows formation of a temporary stoma site around the tube. The initial feedings should either be small amounts (5 ml or less) every 4 hours or CRI (continuous rate infusion) using a syringe pump. The CRI method of feeding will help prevent many of the problems associated with Refeeding Syndrome.

Serum electrolytes, phosphorus and packed cell volume should be monitored closely. A base line value should be established before treatment is started then once daily thereafter, unless dramatic changes are seen. If changes are seen in any of these values, supplementation needs to be started immediately. This can either be intravenous or through the feeding tube. Refeeding Syndrome is one of the most dramatic “side-effects” of hepatic lipidosis and can lead very quickly to death. (1, 2, 4)

Hospital Management
Cats should be allowed out to exercise for 20-30 minutes approximately 1 hour before feeding, 2-3 times daily. This can be started even while the CRI feedings are being done, just disconnect the syringe pump, flush the line with water and cap. Exercise has been found to greatly enhance both gastric motility and patient attitude.

Recovery from hepatic lipidosis typically takes 8-16 weeks (range 4-36 weeks). (2,5,6) Very few cats do poorly after discharge, particularly if good communication is established with the owners and regular rechecks are scheduled. In our practice, rechecks are typically scheduled with the technician managing the case for every 2 weeks until the tube is removed.

Potential Post Discharge Complications
Diarrhea can be seen in cats recovering from Hepatic Lipidosis, and this usually doesn’t start until after discharge from the hospital. If treatment is warranted (the cat is incontinent, the owner is concerned etc), adding canned pumpkin to the diet is beneficial. Since the pumpkin is only available in large cans, advise the clients to use an ice-cube tray to freeze 1-2 tablespoons portions of the pumpkin, and store these in a plastic freezer bag. When needed they can be easily thawed and added to the food. The other end of the spectrum can also be seen, that is the cats become constipated. As they are usually fairly weak from muscle loss and metabolic derangement, the development of constipation is not unexpected. Adding Lactulose to the diet will often solve this problem, 1-2 ml per meal adjust as needed to maintain stool consistency. Sometimes the feeding tubes can become clogged either from insufficient flushing after feeding, or from hair accumulation through the holes in the end of the tube. If the clogging is from insufficient flushing and food is backed up in the tube, first try to flush the clog out using warm water and the feeding syringe. Hold the tube firmly and push the water with force. If the clog is not bad, this may work. If it is still clogged, try switching to Coca-Cola in the feeding tube, and allow this to sit for a period of time. And lastly, what to do about the cat that insists on chewing on its tube? A simple solution is to place a baby’s t-shirt on the cat, usually an infant’s size 6-9 months works well for most cats. Use a t-shirt that has a fitted neck, not the lap shoulders. Once the t-shirt is on, place a piece of 1” porous tape near the end of the feeding tube, tuck the tube up under the t-shirt and use a safety pin to pin the tape to the t-shirt. This makes removal easier for feeding, and decreases the risk of pinning through the tube and damaging it.

Once the cat goes home, tube feedings are continued-even after the cat begins self-feeding. Owners are given instructions to always have fresh food and water available for the convalescing cat and when the desired weight is reached, tube feedings are decreased by 25-50% depending on the cat’s oral intake. The tube is removed after the cat has reached its desired weight and has been totally self-feeding for 2 weeks without showing any signs of weight loss.

Future Considerations
Advise the clients to continue to monitor food intake, this is best accomplished by doing measured feedings, and to call immediately if any decrease is seen. Appetite stimulants can be used to increase food intake, if this is addressed soon enough

Many clients are very reluctant to go through hepatic lipidosis a second time, and are very diligent about feedings and appetite. Continue to support their efforts, and you'll have them around for a long time to come.

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Feeding Tube Management & Complications

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Indications for Tube Use

Does the use of feeding tubes have a place in everyday practice? We are all familiar with the use of feeding tubes for Hepatic Lipidosis cats, but how many times do we deal with the older animal with no obvious physical problem other than an unwillingness to eat adequate (in our opinion) amounts of food? What about the HBC that has a jaw fracture and is having trouble eating enough food to support themselves? As renal failure advances, the animals' appetite often decreases to such a level that this is a bigger concern than the renal failure. An animal being treated for cancer may either develop nausea from the chemotherapy or decreased appetite from the disease. These and many other scenarios are seen routinely in practice and could benefit from the placement of a feeding tube.

Types of Tubes

The most commonly placed feeding tubes are nasoesophageal, esophageal, gastrostomy and jejunostomy. All, with the exception of the nasoesophageal require some level of anesthesia, with the jejunostomy tube usually requiring surgical placement. Nasoesophageal and jejunostomy tubes can only be used under hospital supervision, while esophageal and gastrostomy tubes can be managed by owners at home after the initial reintroduction of food has been done in-hospital.

Esophageal tubes can be placed using minimal equipment following standard technique practices. Gastrostomy tubes can be placed blind using specialized equipment, placed with the aid of a gastroscope (percutaneous endoscopic gastrostomy or PEG) or surgically. Any of these tubes can be placed in any animal that can undergo anesthesia. Anesthesia time is typically 15-20 minutes., and they do not need to achieve a surgical plane of anesthesia, just enough so that jaw tone is lost. Esophageal strictures may preclude endoscopic placement of a feeding tube, but surgical placement can often be done. If the animal is not totally anorexic and not metabolically compromised (i.e. electrolyte disturbances, low phosphorus, low PCV etc) the tube can be placed and the animal discharged from the hospital to the owner's care within 1-3 days.

Feeding can be started immediately with nasoesophageal tube, and within 12 hours esophageal, gastrostomy and jejunostomy tubes. This delay allows a temporary stoma to form around the tube insertion site prior to feeding. A complete feeding plan should be done for each animal with written feeding directions given to the owner. Because many owners are unfamiliar with the use of syringes and the feeding procedure itself, plan on doing an extended discharge for each animal. This should include tube maintenance, feeding directions and feeding amounts; this typically takes 30-45 minutes.

There are multiple veterinary recovery diets that are available in a gruel form that pass easily through most of the larger bore feeding tube (12 fr and higher). Sometimes adding as little as 1-2 tablespoons (15-30 ml) to the can of food will greatly increase ease of passage. If needed, homemade gruel diets can be prepared from commercial diets. The disadvantage of using these diets would be not knowing the caloric amount found in each ml of the final mixture, or the final volume achieved after mixing. These diets also tend to fall out of suspension after they've been mixed with water.

For long term use, place a PEG tube. After a stoma has formed around the rubber feeding tube (usually 3-4 weeks), the tube can be replaced with a low profile or foley type silicone feeding tube. A rubber catheter has a useful life of 12-16 weeks. This is adequate for most hepatic lipidosis cats and post-surgical dogs, but this may not be enough time for a renal failure animal or HBC jaw fracture. The silicone catheters have a useful life of over 1 year, depending on maintenance and care. When they need to be replaced, another silicone catheter can simply be placed in the stoma site.

Mechanical Complications

Mechanical complications include both tube obstruction and premature removal of the tube or dislodgement from the site of placement. The most common problem, tube obstruction can be prevented in most cases by proper tube maintenance. Food should never be allowed to sit in the tube, and the tube should be flushed with warm water after EVERY feeding, or whenever gastrointestinal contents as aspirated through the tube as when checking residuals. When using the feeding tube to administer medications, only one medication at a time should be given through the tube, and it should be given separately from the food. This will help to prevent drug-to-drug interactions as well as drug-to-food interactions as not all medications and enteral foods are compatible with one another.

If the feeding tube becomes clogged either from insufficient flushing after feeding, or from hair accumulation through the holes in the end of the tube, first try to flush the clog out using warm water and the feeding syringe. Hold the tube firmly and push the water with force. If the clog is not bad, this may work. If it is still clogged, try switching to Coca-Cola in the feeding tube, and allow this to sit for a period of time. Some practitioners have suggested the use of pancreatic enzymes mixed with water and various other mixtures instilled into the tube to break up the clog.

This is what I use for stubborn clogs and is 100% effective in removal of the clogs. This tube un-plugging technique can be used with20 fr or larger Pezzer gastrostomy tubes and 20 fr or larger esophagostomy tubes**:**

Use with EXTREME caution…
Supplies:

- 10 fr polypropylene catheter
- 10-12 ml luer slip syringe
- 1" tape

- Cut a bevel on the end of the polypropylene catheter-this will be sharp! Measure the length of the catheter to either the site of the obstruction or the outside of the body wall. Mark with a piece of 1" tape. Do not pass the cut catheter past the body wall-it will perforate the stomach wall!
- Pass the cut catheter to the level of the obstruction; fill the syringe with warm water. Attach the syringe to the tube and use your fingers to pinch around the end of the feeding tube. Flush the water into the catheter with force may need to aspirate and flush repeatedly.
- If the plug has been in the tube for > 12 hours, you may need to carefully "ream" out the plug with the beveled end of the catheter, continue to try to flush the water through the catheter.
- This technique has always worked for me, and I've never had to replace a tube because it was plugged. The sooner the clients bring the animal in the better and quicker the results.

Premature tube removal or dislodgement is best prevented by choosing the most appropriate tube for the animal and using Elizabethan collars and wraps when appropriate. Whenever the location of the tube is in doubt, it should be checked radiographically. While most tubes are radiopaque, a sterile contract media (i.e. Omnipaque) can be infused through the tube to check for leaks into the peritoneal or thoracic cavity.

Gastrointestinal Complications
Some of the gastrointestinal complications seen with tube feeding are related to the feeding itself. Food that is administered too quickly, in too large an amount or at the wrong temperature can all cause nausea, vomiting or abdominal discomfort. These signs can also be related to the patients underlying disease process or a complication of medications the patient is receiving.

Liquid enteral diets are typically very low residue, and are likely to cause a soft stool if not actual diarrhea in a normal animal let alone one who is already ill. Likewise, most recovery diets, both liquid and gruel forms, are high in fat, a patient with impaired fat digestion and absorption may develop steatorrhea when fed these diets.

A cause of diarrhea not typically thought of is the medications that we are giving to the animals, whether they are orally or through the feeding tubes. Many liquid oral forms of medications are hypertonic or contain sorbital, a non-absorbable sugar, and may cause, at least in part diarrhea. We also need to remember that a number of commonly used antibiotics, analgesic agents and other drugs can cause nausea, vomiting and gastrointestinal ileus and may contribute to the discomfort our patients are feeling. Canned pumpkin, 5-15 ml per feeding will usually resolve the diarrhea. This can be prepared in ice cube trays and stored in a freezer bag until needed. The amount of each feeding will need to be adjusted accordingly.

Constipation is not an unusual complication seen in patients with feeding tubes. As they can be fairly weak from muscle loss and metabolic derangement, the development of constipation is not unexpected. Adding Lactulose to the diet will often solve this problem, 1-2 ml per meal adjust as needed to maintain stool consistency.

Metabolic Complications
There are two types of metabolic complications that our patients can develop. The first is the result of the patient's inability to assimilate certain nutrients. This can best be anticipated by doing a proper nutritional assessment of the patient before developing the nutritional plan. The other type is seen with "Refeeding Syndrome".

Keeping in mind the changes the body has undergone while in starvation, when reintroducing food several areas need to be monitored closely to prevent the "Refeeding Syndrome". During recovery, excessively rapid refeeding (or hyperalimentation) can overwhelm the patients already limited functional reserves.

Refeeding causes a shift in the body from a catabolic state where protein is the primary energy source to an anabolic state where carbohydrates are the preferred energy source. Administration of enteral or parenteral nutrition stimulates the release of insulin; this causes dramatic shifts in serum electrolytes from the extracellular space to the intracellular space, primarily phosphorus, potassium and to a lesser degree magnesium. Insulin promotes intracellular uptake of glucose and phosphorus for glycolysis. These electrolyte shifts can have a profound impact on metabolic functions within the body, phosphorus is used by the red blood cells as their primary source of energy in the form of 2,3 DPG, without this they die and you have hemolysis. Phosphorus is integral in the formation of ATP-the power source for most cells within the body, without this they cannot function properly. Potassium is involved in the sodium/potassium pump, without adequate amounts, no muscle contraction/ relaxation can occur. Serum cobalamin is often low in cats that have small intestinal disease, pancreatic disease and hepatic lipidosis . Supplementation may be necessary even before enteral nutrition is started to allow adequate assimilation of nutrients within the intestine. The CRI method of feeding will help prevent many of the problems associated with Refeeding Syndrome.

Serum electrolytes, phosphorus and packed cell volume should be monitored closely. A base line value should be established before treatment is started then once daily thereafter, unless dramatic changes are seen. If changes are seen in any of these values, supplementation needs to be started immediately. This can either be intravenous or through the feeding tube. Refeeding Syndrome is one of the most dramatic “side-effects” and can lead very quickly to death.

Metabolic complications of any type are less likely to occur if estimated caloric needs are conservative. Current recommendations are to initiate feeding at caloric amounts equal to the patient’s calculated resting energy requirements without the addition of any “illness requirements”.

Infectious Complications

The types of infectious complications that can occur in tube fed patients include contamination of the enterally fed formulas, peristomal cellulitis, septic peritonitis and aspiration pneumonia.

Microbial contamination of the food is easily avoided by following basic hygiene in preparation and storage of the food. Blenderized foods should be prepared daily, and opened commercial liquid diets should be kept refrigerated and discarded after 48 hours. When food is being delivered via a syringe pump, no more than 6 hours’ worth of food should be set-up at a time. One of the biggest sources of contamination is inadequate cleaning of equipment used for preparation and delivery of foods. Syringes, containers, and tubing used for preparing, storing and delivering food should be discarded after use. Things that are reused, such as blenders and storage containers, should be cleaned thoroughly and preferably sterilized each time they are used. The equipment used to deliver the food should also be replaced every 24 hours, this includes the syringes and delivery tubes and if the food is hung, the administration bag.

Peristomal cellulitis can be seen with esophagostomy, gastrostomy and jejunostomy tubes. This can usually be avoided by ensuring that the tube is not secured too tightly to the body wall, and by keeping the site clean and protected. Septic peritonitis can develop in patients where the gastrostomy or jejunostomy tube has become dislodge or removed before a permanent stoma had formed. Proper tube selection can help prevent this problem, button or balloon size should be large enough to secure the tube in the stomach lumen. Wraps of Elizabethan collars may be necessary to prevent the patient from accidentally or intentionally prematurely removing the tube. Ensuring that a mature stoma has formed prior to tube removal can help to prevent peritonitis. Patients that are malnourished or are receiving medications that impair would healing may take longer to develop a mature stoma than would healthy patients.

Aspiration pneumonia can be seen with patients that have previously developed aspiration pneumonia, patients with impaired mental status, patients with neurologic injuries, patients with reduced or absent cough or gag reflexes and those on mechanical ventilation. Feeding patients in any of these categories pre-pylorically puts them at risk of aspiration of food. Viable alternatives would include jejunostomy tubes and parenteral nutrition. Lastly, caution should be used when feeding patients with nasoesophageal or esophagostomy tubes using constant rate infusion. These types of tubes can be vomited up and the tip of the tube could relocate in the pharynx and place the patient at risk for pulmonary aspiration.

Hospital Management

Patients should be allowed out to exercise for 20-30 minutes approximately 1 hour before feeding, 2-3 times daily. This can be started even while the CRI feedings are being done, just disconnect the syringe pump, flush the line with water and cap. Exercise has been found to greatly enhance both gastric motility and patient attitude.

Very few patients do poorly after discharge, particularly if good communication is established with the owners and regular rechecks are scheduled. Rechecks should be scheduled with the technician managing the case for every 2 weeks until the tube is removed. If this will be long term maintenance (months to years), these rechecks can become

less frequent and the animal stabilizes and the owners become more comfortable with tube maintenance and management.

Potential Post Discharge Complications

Granulation tissue normally forms around the tube site on the outside and may be quite pink and can even bleed when handled. It is important to let clients know this is normal and to expect it, this tissue is what allows the hole to close after the tube is removed. We have found in cats with dark hair coats (including tabbies) that the hair will grow in a dark ring around the tube site and thicker than the surrounding hair regrowth. Many clients will think that this is necrosis and become very concerned, a quick warning to expect this will greatly ease their minds.

What do you do about the patient that insists on chewing on its tube? A simple solution is to place a baby's t-shirt on a cat, usually an infant's size 6-9 months works well for most. For large patients, larger shirts can be used. Use a t-shirt that has a fitted neck, not the lap shoulders. Once the t-shirt is on, place a piece of 1" porous tape near the end of the feeding tube, tuck the tube up under the t-shirt and use a safety pin to pin the tape to the t-shirt. This makes removal easier for feeding, and decreases the risk of pinning through the tube and damaging it.

Once the patient goes home, tube feedings are continued-even after the patient begins self-feeding. Owners are given instructions to always have fresh food and water available for the convalescing patient and when the desired weight is reached, tube feedings are decreased by 25-50% depending on the oral intake. The tube can be removed after the patient has reached its desired weight, had recovered for the trauma or has finished chemotherapy treatment and has been totally self-feeding for 2 weeks without showing any signs of weight loss. Many feeding tubes can be maintained long term, and the same stoma hole used for repeated tube placements.

Conclusion

Typically, owners are very happy with the results they see when using a feeding tube and the animals feel much better. They do require routine daily care such as cleaning around the tube site and flushing of the feeding tube with water, but the tubes need not be used every day to feed the patient. The use of feeding tubes can give many clients the benefit of enjoying their pet for a longer period of time, and having a better quality of life for both of them.

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NOTES:

Nutritional Management of the Feline CKD Patient

Ed Carlson, CVT, VTS (Nutrition)

Introduction

There are many treatment options for patients with chronic kidney disease (CKD), perhaps none more important than nutritional management with a therapeutic renal diet. Cats with chronic kidney disease can show a variety of clinical signs including but not limited to anorexia, nausea, vomiting, and weight loss. In some cases, cats begin to lose weight before kidney disease is diagnosed making this a particularly important clinical sign to recognize. Multiple studies have shown good quality evidence that the effects of feeding a therapeutic renal diet improve longevity and reduce clinical signs of disease. The goals of nutritional management of chronic kidney disease are to reduce uremia, maintain nitrogen balance by providing optimal protein nutrition, provide non-protein calories, normalize serum phosphorus, and maintain electrolyte balance to slow or lessen clinical signs of the disease including changes in body composition.

Therapeutic Renal Diets

Therapeutic renal diets have restricted protein, phosphorus and sodium levels when compared to maintenance diets. The quality of the protein is extremely important. Diets containing highly digestible protein with the correct balance of amino acids minimize nitrogenous waste. These diets are calorically dense; contain reduced amounts of dietary phosphorus, increased omega-3 fatty acids, antioxidants, B Vitamins, and potassium to help prevent hypokalemia that has been shown to contribute to renal dysfunction and buffers to help control acidemia, which may contribute, to muscle wasting. Protein sources of lesser quality generally contain non-essential amino acids that may be catabolized to urea and may contribute to increased clinical signs in patients with advanced stages of CKD.

What Does the Research Tell Us?

Elliott et al. (2000) found that cats with CKD who were fed a therapeutic renal diet live significantly longer (median survival time of 633 days) compared to cats in the control group who were fed a maintenance diet (264 days). In another randomized, double-blind study, cats in the control group suffered 26% more uremic episodes compared to those fed a therapeutic renal diet. None of the cats fed the renal diet died during the study however 22% of the cats in the control group died. (Ross, et al. 2006) According to Jessica Quimby, DVM, Ph.D., DACVIM, "…based on published evidence, feeding a dietetic renal food is the single most effective management option for improving survival and quality of life in dogs and cats with CKD. While new emerging evidence increases on the benefits of dietetic renal food in dogs with IRIS-Stage 1 CKD, more research is needed to confirm the most optimal nutritional management in early stages of the disease."

What about muscle wasting? Aren't renal diets too low in protein? No, most renal diets fall within the AAFCO minimum requirements for adult maintenance diets for healthy cats. There is no evidence to support the premise that cats eating renal diets will lose muscle weight or body weight if the patient is eating their daily caloric requirements of the therapeutic renal diet. In a 2-year randomized controlled clinical trial (Ross, et al 2006) no difference in body condition score or body weight was seen when comparing cats suffering from CKD eating a renal diet to those eating a maintenance diet.

Restricting dietary phosphorous has been shown to help slow the progression of renal disease. Several studies have shown feeding therapeutic veterinary diets increases survival rates and have been associated with significantly reducing plasma phosphorus and PTH levels compared to patients fed diets higher in phosphorus. As renal disease progresses it may become impossible to keep phosphorus concentrations within the IRIS guidelines using diet alone. If serum phosphorous remains high, 4 weeks after transiting to a therapeutic renal diet, a phosphate binder should be considered.

High levels of sodium in diets fed to patients with chronic kidney disease may cause sodium retention with the expansion of extracellular fluid volume and can cause hypertension, fluid overload, and edema. However, excessively limiting dietary sodium may cause a negative sodium balance resulting in reduced extracellular fluid volume, plasma volume, and glomerular filtration rate (GFR). Dietary sodium has been shown to have no impact on blood pressure in dogs and cats. Restricting sodium may contribute to muscle wasting in cats.

Cats with chronic kidney disease are prone to potassium deficiency. Decreased potassium levels may be caused by anorexia, vomiting, and increased urinary losses due to polyuria. Serum potassium should be monitored and supplemented when necessary. For cats with hypokalemia, oral supplementation with potassium gluconate should be considered if diet alone does not maintain serum potassium concentration above 4.0mEq/l (Polzin, 2007). Oral administration is safest and is the preferred method unless a critical emergency exists or if oral administration is

impossible or contraindicated. Oral potassium gluconate appears to be tolerated well by most patients. The dose is adjusted based on the patient's clinical signs and serum potassium levels, which initially should be checked every 2 to 4 days until stable and then every 2 to 4 weeks thereafter.

Feeding the CKD Patient

The daily energy requirement (DER) for cats with CKD is 1.1 to 1.4 times the patient's resting energy requirement (RER). A gradual transition, over 3 to 4 weeks or more, for cats is recommended to potentially slow the change in decrease urinary sodium levels that often accompany renal dysfunction. The author cannot stress enough the importance of educating owners on the importance of feeding appropriate diets to these patients and the need to transition gradually! Cats, in particular, can be resistant to diet changes. Some patients may be less resistant to a diet change when transitioned at a slow rate. Some patients accept new foods more easily if the new and old diets are offered in separate side-by-side dishes than if the diets are combined in one dish. Some cats seem to be more accepting of a new diet if it is offered in a flat dish rather than a bowl, even if they normally eat in a bowl. This may have to do with their whiskers rubbing on the sides of the dish, something that does not happen when they eat from a plate. Sometimes adding low sodium tuna juice or chicken broth to a renal diet to encourage patients to eat the new food works. This may be gradually eliminated once they become accustomed to the new food. Also, sometimes just adding additional water to the new food will encourage the canine and feline patient to eat. Warming the food sometimes increases palatability with some patients. In some cases, pharmacologic intervention may be considered.

It is not usual for the CKD patient to only eat a small amount of food or to stop eating altogether. Patients exhibiting signs of nausea should be prescribed antiemetics. In a survey conducted in 2015 of owners of cats with CKD, reduced appetite was reported by 43% of owners. 77% of those owners coaxed their cat to eat 50% of the time. CKD patients that do not consume their daily caloric requirement will suffer muscle loss as it is catabolized to provide energy to the body. Reduced food intake also means the patient is not consuming adequate protein that will also lead to muscle loss. Pharmacological intervention to prevent and manage change in body composition including weight loss can be instituted in cases where even subtle changes are detected. A medication to manage unintended weight loss is available in a transdermal formulation made specifically for cats.

Another, often underutilized, option is the use of an esophageal feeding tube. E-tubes can extend a patient's life and improve not only the quality of life of the patient, but also the quality of life of the owner. Veterinary therapeutic diets may be made into slurry and clients are able to easily manage assisted feeding at home. Clients are also easily able to administer the multiple medications that many chronic kidney disease patients have been prescribed via the feeding, often more easily than by mouth. Additional water may be administered via the feeding tube that can eliminate the need for subcutaneous fluids; not only is this easier for most clients but is more easily used by the body.

Nursing Care

Providing excellent nursing care and being a patient advocate are perhaps the most important two roles of the veterinary technician!

Hospitalized CKD patients should have water available even when on IV fluids unless they are actively vomiting, are NPO prior to surgery, or have another medical reason that requires water be withheld. Watch these patients for signs of nausea -- drooling and/or looking away from food when offered -- as these are two signs your patient may be nauseous. Bring this to the veterinarian's attention and request they prescribe anti-nausea medication. Do not leave food in the cage with a nauseous patient, rather offer small amounts of food frequently and remove it after a few minutes if the patient shows no interest in eating. Discuss the possibility of placing a feeding tube with the veterinarian. Anorexia is very common in dogs and cats suffering from chronic kidney disease. Food, most medications, and water can be administered via a feeding tube. Placement of a feeding tube may help to extend the life of a patient with CKD and provide improved quality of life for the patient and the owner. If weight loss is noted this should also be discussed with the veterinarian as a medication to help manage unintended weight loss can be prescribed.

Avoid introducing therapeutic renal diets to patients in the hospital as this can cause food aversion. Wait until the patient is feeling better and ideally has been home from the hospital and eating well for a few days before starting to transition to a therapeutic diet. Avoid force-feeding, especially nauseous patients as this may also cause a food aversion! Be a patient advocate and discuss placing a feeding tube with the veterinarian if possible, rather than force-feeding.

Provide client education and support to owners of patients that are suffering from chronic kidney disease. Avoid sending home a variety of therapeutic diets with clients in the hope that the patient will "like" one. Diet options are limited for these patients; offering multiple choices can cause a food aversion. Select the diet best suited for the patient and encourage the owner to be patient, allowing their pet time to adjust to the new diet. Educate owners on the importance of allowing their pet to have access to clean, fresh water at all times. Patients with CKD often drink more; they may

require a larger water bowl or multiple bowls to ensure they have water available at all times. Explain the importance of feeding a veterinary therapeutic renal diet and that it has been shown to slow the progression of the disease. Most chronic kidney disease patients become anorexic at some point as the disease progresses and they may also continue to lose weight. Management of their clinical signs is paramount and medication to manage unintended weight loss should be considered if warranted, throughout the disease process. Explain this to clients when their pet is first diagnosed with CKD. Introduce them to the idea of a feeding tube being placed in the future.,Explain the benefits and, if possible, offer to put them in touch with another client that uses or has used a feeding tube (provided, of course, that you have the clients' permission to do so). Share your favorite tricks for encouraging a patient to eat when they are not interested in food. Likewise discuss the possibility that medication may be prescribed to manage unintended weight loss as it occurs with disease progression. Owners can be taught to monitor body and muscle condition scores at home in order to help identify changes.

Uremic breath with or without excessive drooling is often an indication of oral ulcers that are not uncommon in CKD patients especially in the later stages of the disease. Oral rinses containing topical pain medications, designed for veterinary patients, are commercially available. Monitor CKD patients for possible oral ulcers and bring your suspicions to the veterinarians' attention and suggest they prescribe these products if appropriate.

In conclusion, remember patients don't eat when they feel better, they feel better when they eat! Be a nutritional advocate for your patients!

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Nutrition for the Hospitalized Veterinary Patient

Ed Carlson, CVT, VTS (Nutrition)

Introduction

Nutrition is vitally important to the hospitalized feline veterinary patient! Unfortunately, the nutritional needs of hospitalized cats are sometimes overlooked. Doctors' orders might not be specific or might not include feeding or routine body weight measurement instructions. The patient might be unwilling to eat, unable to eat, or only consuming a small amount of food and may have already started to show signs of subsequent weight loss prior to hospitalization. Whatever the reason, as patient advocates, veterinary technicians and veterinary nurses should take a primary role to ensure that the patients' nutritional needs are met.

The Importance of Nutrition for the Hospitalized Veterinary Patient

Daily proper nutrients are crucial to maintain optimal immune function, for normal cellular structure and function and drug metabolism. Cats that do not consume adequate nutrition are prone to lean body mass loss and its negative effects which may include a negative impact on overall survival and lifespan (Teng et al 2018). Hospitalized cats, particularly the critically ill, who are not receiving adequate nutrition are at risk for organ dysfunction, weakness, delay wound healing, may have an increase in the occurrence of acquired infections and potential for bacterial translocation. Bacterial translocation is defined as the passage of viable bacteria from the intestines to extraintestinal sites. It is believed that reduced perfusion and impaired oxygen delivery to the gastrointestinal tract results in increased intestinal permeability, leading to translocation of normal intestinal flora. Research has shown that the addition of glutamine, arginine and omega-3 fatty acids can augment intestinal barrier function and prevent bacterial translocation. While improved clinical outcome in veterinary patients receiving adequate nutrition has not been definitively proven, malnutrition in critically ill people has been shown to have a negative impact on patient outcomes.

Dietary Considerations

Healthy cats use, and store energy derived from carbohydrates very effectively. However, in an unhealthy state reduced GI absorptive, reduced digestive enzyme production, and insulin resistance may impact dietary carbohydrate tolerance which may result in altered glucose control and/or diarrhea. Diets formulated for recovery often have a low carbohydrate content**.** It is important to provide critical patients with adequate dietary protein that supplies essential amino acids. High dietary protein may be used in place of carbohydrates in critical feline and canine patients who are not able handle carbohydrates well. High protein is contraindicated in patients with hepatic and renal disease. Calories provided from fat are equally important in the critical patient. Fat is more calorically dense than protein or carbohydrates therefore patients may ingest a smaller volume of food while still receiving more calories. High fat content is contraindicated in patients suffer from pancreatitis. Arginine, an amino acid, is essential to protein synthesis and has an immune-preserving effect on protein malnutrition. Glutamine, also an amino acid, plays a role in protein metabolism, nutrient absorption, and intestinal immune function. Folic acid, thiamin, riboflavin, niacin, pantothenic acid, pyridoxine and B12 are required for the metabolism of protein, fat, and glucose. Patients consuming their resting energy requirement (RER) of a commercial diet should be receiving an adequate amount of these. However, patients who are not eating should be supplemented with B vitamins in IV fluids or parenteral nutrition.

Enteral feeding is preferred in patients who can tolerate it. Patients exhibiting signs of nausea should be prescribed antiemetics. Pharmacological intervention to prevent and manage weight loss should be considered. Feedings tubes should be considered in patients that are unwilling to eat or unable to eat. Nasogastric feeding tubes are easily placed without anesthesia and are often a good option in critical patients allowing for trickle feeding of a liquid diet. Force feeding may cause food aversion and should be avoided. Obtaining a nutritional history, including how long the patient has been anorexic at home prior to being admitted to the veterinary hospital, is crucial. Patients that have been anorexic for 3 or more days should be provided with nutritional support. Parental nutrition should be considered in patients that are unable to tolerate feeding by mouth.

Energy Requirements

Resting energy requirement (RER) represents the energy requirement for a normal animal, which is not fasted, and is at rest under thermo-neutral conditions. The equation 70 x (body weight in kg) ¾ = RER or √√ x (wt. in kg x wt. in kg x wt. in kg) = x 70 = RER are used to calculate the resting energy requirement for the critical patient. The general recommendation to begin enteral feeding anorexic patients is one third of the patient's total RER for the first 12 hours and, if well tolerated, to gradually increase this amount every 12 hours until full RER is reached. If at any time the patient vomits, discontinuing feeding until vomiting has resolved, reducing the volume when feeding is resumed, and increasing the volume more slowly is recommended. In the past, an illness factor was often added to the RER when

feeding critically ill patients, however this practice is no longer recommended. It has been shown that excessive nutrition during times of illness may increase the risk of hyperglycemia and other metabolic complications.

Nasogastric (NG) and Nasoesphageal (NE) Tube Feeding

Only liquid veterinary diets should be used for feeding through NG and NE tubes. Trickle feeding via constant rate infusion (CRI) is often used for hospitalized patients, although these tubes may also be used for bolus feedings and to administer oral liquid medications. Tablets should not be crushed and administered via these small tubes. A number of liquid diets designed for people are also available. These diets are typically less expensive then veterinary liquid diets, however, are nutritionally inadequate and some may contain ingredients that are inappropriate for dogs and cats. These human diets are especially inappropriate for cats as they are too low in protein, taurine, and arginine.

Parenteral Nutrition

Parenteral nutrition (PN) is a nutritional balanced solution that provides calories and nutrients to patients that cannot tolerate enteral nutrition or should not be fed by mouth. Total parenteral nutrition (TPN) provides all caloric, protein and micronutrient requirements and should only be administered via a central venous catheter due to its high osmolality. Partial parenteral nutrition (PPN) provides only part a patient's caloric, protein and nutrient requirements however has a lower osmolality and therefore may be administered via peripheral IV catheters. Complications associated with the use of parenteral nutrition include hyperglycemia, hyperlipidemia, potential risk of infection, intestinal atrophy, with subsequent risk of bacterial translocation, increased rate of sepsis, and blood electrolyte abnormalities. Aseptic technique is required, and extreme care should be taken with the handling and administration of parenteral nutrition; if contaminated PN can become an excellent growth medium for bacteria. A study by Jensen and Chan (2014) showed patients receiving PN that were also trickle fed had a higher survival rate than those receiving PN only. If PN is used, the general recommendation is to begin trickle feeding as soon as the patient will tolerate it and gradually increase enteral feeding.

Nursing Care

Experienced veterinary technicians and veterinary nurses generally use a variety of coaxing techniques to encourage their patients to eat. Warming a canned food may work for some patients while chilling a canned food may be better accepted by nauseous patients. Hand feeding, petting and talking to the patient in a soothing manner during feeding time may work with some patients while others may prefer to eat when left alone and undisturbed. Whatever methods are used to encourage eating, good record keeping is essential to determine if the patient is consuming adequate calories or if assisted feeding should be initiated. Nursing notes should include what specific food was offered, volume of food offered, approximate volume of food consumed, and calories consumed. Additionally, medications to help manage unintended weight loss can also be administered. It's important to monitor patient body composition closely during hospitalization, specifically taking note of body condition, muscle condition, and body weight throughout the patient stay. An FDA approved transdermal medication is available for cats to help manage unintended weight loss and can be considered an adjunct part of a multi-modal approach to feline patient care.

Conclusion

The goal of nutritional support for the hospitalized feline patient is to prevent or minimize malnutrition and changes in body composition, restore nutrient deficiencies and provide nutrients to promote healing. Veterinary technicians and veterinary nurses play an essential role in monitoring and providing nutritional support to critical patients that may improve patient outcome.

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Feline Pain Management: Using Physical Rehabilitation Treatments & Modalities

Kristen Hagler, BS, RVT, VTS, CCRP, CVPP, OACM, CBW

Introduction

Since the 1990's canine and equine species have dominated physical rehabilitation in both marketing and research however treatment of the feline patient is gaining momentum and interest as practitioners discover a remarkably well response to treatments and therapeutic principles. It is thought this "forgotten feline" mindset is attributed to apparent independence of the species, the ability to cope with physical disability, and significant differences in behavioral characteristics and temperaments make pain assessment challenging from patient to patient. Through research and studying individual species, we have come to better understand pain physiology for the feline patient which includes a growing toolbox of complementary modalities and therapeutics to be used in the multi-modal pain approach. Working with the feline patient can also be quite unique because certain behavioral attributes such as the low desire to please humans, decreased attention span and fickle motivators are present when compared to other species but with adjustments, physical rehabilitation techniques can be quite successful.

Pain Recognition and Assessment

The first line of defense in any treatment plan of pain is recognition of pain. In the feline patient, conditions such as obesity, osteoarthritis, dental and gum disease, neoplasia, interstitial cystitis, dermatitis, and chronic wounds contribute to chronic pain (Robertson SA. 2008). Pain can be divided into two general categories classified as adaptive and maladaptive. Adaptive pain protects the body from injury and promotes healing by inhibiting activity when it occurs. This is also known as acute pain and in cat's trauma or postoperative pain is most commonly associated but other causes such as neurological disease, thrombic events, lower urinary tract disease, pancreatitis, or obstipation should be investigated as potential sources if the cause is not readily apparent. Maladaptive pain is a reflection of the pathologic activity within the nervous system that lingers and is more difficult to eliminate. Chronic maladaptive pain has more recently been defined as pain that extends beyond normal tissue healing and/or can be identified with low levels of identified pathology that is insufficient to explain the presence and/or extent of pain (Jacobson L. 2001). Adaptive pain can progress to maladaptive and occurs over a spectrum of events ultimately leading to a condition called windup, a progressive increase in action potential output from the dorsal horn neurons elicited during the course of prolonged, repeated low-frequency C-fiber or nociceptor stimuli (Fox SM. 2004).

Pain assessment is a critical component in determining the well-being of an animal and must be done on an individual basis. Veterinary patients are non-verbal and cannot express feelings in a direct manner for consistent interpretation making treatment planning challenging. In humans, visual analog and numerical scales can be used to help describe pain and assign a score based on physical and emotional responses but in the veterinary patient assessment of pain comes with challenges including: observer bias for pain perception, assumption, observer subjectivity, inter-observer variability or lack of standardized intervention points (Norkin CC. 1995) and inter-species variability. For animal patient's laboratory testing methods, physical examination findings, behavioral assessments and trends in activity must all be used in combination to develop a working diagnosis and therapeutic treatment plan. In the author's experience, less than 10% of veterinary hospitals employ pain scoring systems or know how to consistently assess pain in clinical practice. The most accurate and reliable way to evaluate pain is through behavior and emotive assessment. A change in behavior or habit is often the only sign of pain in animals and can be difficult to assess. Responses may be influenced by the presence of other animals and humans, environment, anxiety, fear, hunger, or medication side-effects. A thorough history including normal behavior, development of any new behaviors and cessation of previous behaviors. Activity tendencies including eating habits (increased, decreased, finicky), territory range (reduced, wandering and not returning), interactions with other animals and people (hissing, growling, avoidance, meowing), changes in facial expressions (grimaces, flattened ears, glazed eyes, mydriasis), grooming habits (increased, lack of, sensitivity when brushed, self-trauma), posture preferences (lying down or sitting often, arched backs, low head carriage, abnormal tail position, decreased weightbearing), agility (not jumping anymore, avoidance of stairs, laps, tunnels) and sleeping preferences (increased, decreased, interrupted) all help determine pain levels in cats.

To help mitigate external stressors or influencers in the clinical setting pre-evaluation planning is recommended. The environment should be prepared solely to appease the patient species and pheromones should be used wherever patients are to be examined and treatments performed. A pheromone called Feliway® can have a marked effect on some pets (Yin S. 2009) and can be sprayed on towels, personnel attire or diffused in the treatment area prior to a pet's arrival to help reduce stress and anxiety. When possible, a single species environment with limited to no interaction between other animals reduces flight responses associated with unfamiliar sights, smells and sounds. Whenever possible, the feline patient should be allowed to stay in the carrier (with portions removed for examination

access) should they choose, have access to exit routes or safe spots in the area while still allowing procedures to be completed or methods for taking brain breaks such as climbing towers, tunnels, toys or treats available. When the feline patient chooses to utilize brain breaks in the examination room, attention is paid to the physical characteristics of movement and noted in the medical record. When appropriate handling should be minimally performed and in order of the most, to least critical for accurate diagnosis to keep even tolerance levels during examination. If aspects of the examination are unable to be performed but are still required for proper medical diagnosis, the patient should return another day to prevent further escalation in stress. Towels, wraps, carrying bags, visual blockades or other means of creating a low stress experience for the cat should also be considered.

Pain Scoring

An effective pain management treatment plan regular pain scoring every visit, every time. Pain scales should be used in conjunction with a thorough physical examination and history to assess every patient individually (Fox SM. 2004). It is critical for all team members to be familiar with the scoring method chosen for the hospital and in some cases, it is more appropriate to develop a scoring system extrapolated from established scales fitting the needs of the hospital and team. The International Association on the Study of Pain (IASP) best describes pain for non-verbal patients as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (or described in terms of such damage). Pain is initiated by stimulation of nociceptors in the peripheral nervous system or by damage to or malfunction of the peripheral or central nervous system (Woolf CJ. 1999). Treatment of pain in animals becomes easier with recognition of pain responses; those that modify the animal's behavior by learning and avoiding the experience, those that are automatic and protect the animal, those that minimize pain and assist healing and those that are designed to elicit help or to stop another animal from inflicting more pain (Anil SS. *et al.* 2002). Simple scoring systems include Visual Analog Scales (VAS), Numerical Rating Scales (NRS) and Simple Descriptive Scales (SDS) which are unidimensional. Complex scoring systems include multifactorial or composite pain scales are more ideal because several aspects of pain intensity and pain related disability are included. Multidimensional scoring systems for feline patients include the following:

- Colorado State University: Dynamic Interactive-VAS. Acute pain scale. Numeric, categoric, and convenient to use in the clinical setting. Requires minimal interpretation. Incorporates physiological and behavioral assessments in addition to responses to wound palpation and general body tension (Muir and Gaynor, 2002)
- Glasgow Composite Pain Scale (GCPS): Subjective Descriptive Scale. Acute pain scale. Includes various dimensions of pain (multidimensional) and is thought to be more useful in indicating how much the pain is "meant" to the animal in addition to giving evaluators more assessment options. Three caricatures sequenced as facial expressions using ear position and muzzle/cheek shape used to rate pain. Scoring scales are used for ear position and nose/muzzle shape independently. Standardized mouth and ear distances when combined showed excellent discrimination, correctly differentiating pain-free and painful cats in 98% of cases (Holden E. *et al.* 2014).
- Feline Musculoskeletal Pain Index (FMPI): Chronic pain scale. The only multifactorial clinical measurement instrument (Goldberg ME, 2018).
- Vetergesic® Multidimensional Composite Pain Scare (MDCPS) – Alstoe Animal Health, UK: Acute post-operative pain. Interactive and non-interactive assessments including behavior. Each factor enables observers to sub-score and evaluate each separately.
- UNSEP-Botucatu MDCPS: Acute post-operative pain. Validation of scare in review. Incorporates posture, behavior, reaction to surgical wound palpation, appetite. Observer interpretation required.

Assessing Outcomes

Normal joint motion has been well described for other species (Jaegger G. 2002) and can be used to assess joint health in the feline patient. Normal range of motion (ROM) is required for normal function and when compromised the body increases movement at another segment. This hypermobility can lead to abnormal localized stress causing pain and eventually laxity which can lead to injury depending on activity level. Other secondary conditions such as myofascial tissue dysfunction and osteoarthritis can develop from chronic compensatory postures, abnormal, activity, muscular soreness and asymmetry. Joint motion angles can be objectively quantified to help assess severity of disease using a tool called a goniometer. Goniometry is the qualitative angle measurement of the joint axis obtained by positioning the two arms of a goniometer along the bones immediately proximal and distal to the joint being examined. The two arms of the goniometer are lined up with specific anatomical landmarks for each joint (Jaeger GH. *et.al* 2007) with movement measured in both flexion and extension.

Muscular fitness is an indication of overall physical activity from the previous two weeks of activity and can also indicate should be routinely assessed as part of the physical examination especially after a period of convalescence. The pelvic limbs provide propulsion and power for directional changes when running and jumping and the thoracic limbs provide lift when jumping, agility for climbing and permit significant range of motion. In the feline patient, the need for agility and speed is a critical component to maintain normal feline behavior in stalking prey, climbing or

socializing. Muscle mass circumference changes are related to increases or decreases in strength, correlate with overall body conditioning and reflect overall body weight distribution. Muscle condition scoring can be affected by overall disease or aging and should also be utilized for a complete picture of muscular fitness and health. The World Small Animal Veterinary Association Global Nutrition Committee guidelines (2013) state muscle loss typically is noted first in the epaxial muscles; with muscle loss at other sites being more variable. Scoring includes visual examination and palpation over the following areas: temporal bones, scapulae, lumbar vertebrae and pelvic bones (Burns. K. 2018). Muscle condition scores are graded as normal, mild, moderate, or severe loss. Girth circumference of the limbs, the thigh and forelimb, are obtained using a measuring tape with spring tension to indirectly assess muscle mass. Following guidelines used in one study (Millis DL. 1999), thigh circumference is determined at a point 70% of upper limb length and is measured in centimeters (cm). Another method suggests snugly placing the tension tape in the groin and using the greater trochanter as a landmark to obtain girth measurements (Sprague S. 2013). Antebrachial flexor and extensor muscles of the forelimb are measured by placing the tension tape at the muscle belly center of the extensor carpi radialis. The triceps muscle, an important anti-gravity muscle, is assessed just above the lateral epicondyle of the humerus where the muscle group transitions into the tendon, inserting onto the olecranon process of the ulna. Shoulder muscle assessment (e.g. the deltoids) requires the measuring tape bring placed snugly in the axilla, using the acromion process as a landmark to obtain girth. Finally, thoracic girth circumference measurements may also be useful in body condition scoring. The tension tape is wrapped around the thorax, using thoracic vertebrae 11 and the xyphoid process as landmarks and recorded. For overweight and obese pets, this single measurement may be a useful tool in objective assessments and owner compliance.

Additional Factors Contributing to Disability and Pain

Obesity in small animal patients has reached epidemic proportions in the United States. Thirty-five percent of adult pets and 50% of pets over the age of seven are considered overweight or obese (German, AJ. *et. al. 2006)*. Multiple factors influence these statistics including an overall sedentary lifestyle, increased numbers of people living in cities or urban areas without outdoor access, increased caloric intake and varied feeding guidelines for commercial foods, and genetic susceptibility. Obesity is a condition caused by an imbalance of energy intake and energy expenditure and can be easily prevented. Excess body weight increases health risks for early arthritis development, diabetes mellitus, cancer, skin disease, lower urinary tract disease, hepatic lipidosis and heart disease. Evaluation of weight and nutrition starts with an accurate recognition of obesity and ideal body condition scoring (BCS) measuring fat. Nutritional management starts with a comprehensive history and thorough physical examination. Overall caloric intake, including all sources of food, who is feeding and how the pet is being fed are all discussed. Body condition charts help visualize optimum weight on pets for pet owners and daily nutrition charts assist with feeding compliance by family members. It is recommended for animals on a weight loss program to be weighed at least weekly, ensuring goals are met and weight loss over 1% of ideal body weight does not occur. For feline patients, weight checks may be done at home on a bathroom scale with reporting to the veterinary team over the phone instead of visiting the veterinary hospital.

In addition to obesity associated health risks, animals may be unable to participate in normal pleasure or grooming activities. For feline patient's, the inability to perform such activities may affect overall quality of life, social interactions with family members and household manners. Cats are an independent species and rely on agility to perform a variety of essential physical functions such as grooming, stalking prey, climbing trees, burying their feces, being able to right themselves when falling and jumping on/off of ledges and defend a territory. Obese or overweight feline patients are more likely to have difficulty performing these daily life activities which may cause depression, promote reduced activity, cause injury or other development of other healthcare problems and affect the human-animal bond.

Rehabilitative Therapies

Thermal Therapies

Superficial thermal agents are used to alter cellular metabolism and provide pain management through the physical laws of heat transfer, conduction and radiation. Cryotherapy (cold therapy) refers to the application of cold as a method of rehabilitation during the inflammatory phase to reduce metabolic rate of injured tissues. During cryotherapy, heat energy transfers from bodily tissues to the cold modality via conduction (direct contact between the body and cold pack) and when compared to heat, is a much longer acting physical agent modality. Sustained effects from cryotherapy occur from decreases in local circulation, edema formation, hemorrhage, histamine release, cellular metabolism, muscle spindle activity, sensory and motor nerve conduction velocity, spasticity, and pain with skin temperature and underling tissues being cooled to a depth of ~2 to 4 cm. Superficial thermal therapy delivered as heat contains properties that are opposite those of cold. Heat is retained by tissues through energy transfer moving from the warmer object (the thermal agent) to the cooler object (the body). The energy transfer is carried away by local circulation quickly, causing tissues to lose any changes in temperature for shorter lengths of time when compared to those retained by cryotherapy. Heat therapy sources are classified as radiant, conductive, or convective and for most veterinary applications conductive heat therapy (warm packs) is used. Physiological effects from local

application of superficial thermal therapy includes decreases in blood pressure, muscle spasm and pain while increases occur in body temperature, respiratory rate, capillary pressure and permeability, muscle relaxation, tissue elasticity, local circulation, and leukocyte migration. Superficial heat therapy penetration can be achieved through warm packs and whirlpool baths, penetrating about 2 cm into tissues. Heat therapy alters the neurophysiology order of sensation by elevating the cutaneous thermal receptor pain threshold, inhibiting pain transmission at the dorsal horn of the spinal cord.

Photobiomodulation/Therapeutic Laser

Therapeutic laser alters cellular function by modulating a process known as photobiostimulation. It is defined as a non-thermal interaction of monochromatic radiation within a target site, stimulating cellular mechanisms like mitochondrial respiration and adenosine triphosphate (ATP) synthesis to accelerate healing or regeneration. The most common application of photobiomodulation (PBM) is as an adjunctive therapy in the management of chronic pain conditions like osteoarthritis. It is also is used for musculoskeletal, tendon, or ligament injury, reduction of scar tissue formation, treatment of myofascial trigger points, stimulation or sedation of acupuncture points, improvement of chronic or acute skin wound healing times, reduction of localized bacterial counts, improved vascular and lymphatic flow, stimulation of nerve regeneration, and pain management. Most cats tolerate PBM treatments well, with few patients reacting to subtle fluctuations in sensation as energy is delivered to the tissues. This is often seen in patients with acute conditions, while tissues are acutely healing or in longstanding arthritis. During treatment, the therapist may observe a panniculus reflex in the local dermatome, the patient shifting its body around, looking at the treatment area suddenly or general avoidance. If these symptoms occur, the prescribing veterinarian should be notified to alter the treatment program.

Electromagnetic Field Therapy

Magnet therapy in the treatment of various medical conditions dates back as early as 200 AD with Greek healers reportedly using magnetic rings as a treatment for arthritis (Basford JR. 2001). There are several forms of magnet therapy available for use in the alleviation of pain and promotion of healing. Delivery forms of treatment includes bedding, collars jackets, rings, wraps and others. Current literature is sparse and weak evidence exists for the claims to effect pain, blood flow, tissue oxygenation, bone and tissue regeneration, inflammation and sleep. The small number of studies that do exist for the effects of pain alleviation and bone or wound healing are theorized to cause changes in blood flow and selectively attenuate neuronal depolarization by shifting resting membrane potential. Pulsed electromagnetic field (PEMF) electromagnetism is generated by running an electric current through a coiled wire and are hyposensitized to have an electric rather than magnetic effect on tissue. Stimulation by PEMF may act of cell surface receptors and secondary messengers in addition to having a potential stabilizing effect on intracellular calcium stores. There is a larger amount of supportive evidence for PEMF therapy in the treatment for certain conditions like osteoarthritis, acute surgical pain and wound healing. Regular use in veterinary medicine is hampered by the lack of prospective, blinded, placebo-controlled studies (Millis DL. 2014) but pet owners are willing to use PEMF therapy because pets can be treated in the home and they are seeing positive effects. Treatment times can vary between manufacturers and each PEMF unit utilizes proprietary pulsed frequencies. Animals must remain still during treatment and must be treated several times a day to retain therapeutic effects. There are no known side effects from PEMF therapy, but some animals may experience a tingling sensation if a chronic injury is considered acute or if they are sensitive to stimulation in general (e.g. acupuncture, electrical muscle stimulation, PBM).

Manual Therapy

Therapeutic massage has positive influences on the physical and psychological well-being of animals of all ages and conditions, aides with pain relief and improves mobility. Pain relief occurs from an increase in the pain threshold and a release of systemic endorphins once relaxation occurs, increase of blood flow and oxygen supply to muscles, resolution of muscle spasms, increase elasticity of tendons and ligaments, improve joint and muscle function, and prevent tissue adhesions after surgery or injury (Medina CM. 2018). These mechanical effects occur from actual physical contact caused by pressure applied on the body and is directly proportional to the amount of pressure applied to tissues. Reflex effects occurring from therapeutic massage are based on peripheral receptor stimulation producing central effects of relaxation and is achieved with a very light touch stimulating cutaneous sensory nerve endings. Therapeutic massage techniques include the hold, stroke, effleurage and petrissage. Each technique holds a specific therapeutic goal during application and duration of treatment is often guided by the patient. In the management of chronic conditions, patients often require therapeutic massage two to three times a week while acute conditions may require up to every two to four hours until the condition improves. The duration of a massage session is often dictated by the tolerance of the cat with a range of 5-20 minutes.

Range of Motion (ROM) exercises are useful in diminishing the effects of disuse and immobilization after surgical procedures and is one of the most important aspects of any physical rehabilitation program aside from active therapeutic ROM exercise. In order to maintain normal ROM, joints and muscles must periodically be moved throughout their available ranges or the tissues develop fibrotic adhesions restricting joint motion. Passive ROM is

motion of a joint that is performed without muscle contraction and remains within the patient's available ROM, using an external force to move the joint in a proper plane of movement. It should be used whenever a patient is unable to move joints on its own or active motion is contraindicated. The patient should remain pain free during the therapy time and not react negatively to movements. Over-aggressive ROM exercise will result in pain, reflex inhibition, delayed use of the limb, and more fibrosis of the tissues around the joint. Passive ROM therapy cannot prevent muscle atrophy, increase strength and endurance, or assist with circulation to the extent that voluntary muscle contraction does.

Therapeutic Exercise

Although a well-established method to measure fitness levels in animals is yet to be developed, we do know muscular fitness represents the previous two weeks of activity and can be assessed through physical testing. Fitness is defined as the ability to perform a variety of exercises, and activities and can be objectively measured in animals. Exercise in humans has been proven to have both psychological and physical benefits including, extension of health and lifespan and psychological effects of exercise being powerful enough to be considered a psychoactive drug (Zink CM. 2013). Using concepts from canine conditioning and training programs, feline patients can be assessed for overall strength, proprioception, core strength and skill. Muscle scoring systems, although subjective, help assign a numerical score. This includes a rating system from 1 to 3 for muscular zones including the deltoids and triceps, latissimus dorsi, external abdominals, gluteal and hamstring muscles. Areas scoring one (1) indicate a lower muscular fitness. Muscles are soft, depressible and have poorly defined muscle bellies. Areas scoring three (3) indicate high fitness with firm, springy and well-defined muscle bellies. Muscle groups should be evaluated and scored individually to obtain an overall fitness score, then checked at regular intervals when the patient achieves a weight loss or fitness milestone. Feline patients typically engage in species specific activities which could benefit from a fitness program. Patients should always be assessed individually along with environmental needs (e.g. an animal should never be trained to jump on and off obstacles if they live in a single level environment). Exercise programs including range of motion and stretching activities, aerobic conditioning, muscle strengthening, and skill training are ideal for successful outcomes. Fitness activities are modified by first increasing the frequency of activity and allowing adequate rest periods between sessions. After appropriate adaptation and conditioning have occurred, the length of activity is increased to provide further challenges. A general rule of thumb when advancing any exercise program is to increase activities 10-15% per week until exercise goals are met.

Therapeutic exercise is a critical component to any physical rehabilitation program to help encourage use of muscles, improve joint motion, proprioception and flexibility but requires creativity when applied to feline patients. For most conditions, exercises should be done on a daily basis, including at least two dedicated short exercise periods per day. In a clinical setting, special considerations for feline exercise programs include patience, a calm considerate approach, short exercise periods to prevent boredom, promoting minimal handling and an environment with minimal distractions or exit routes (Goldberg ME. 2018). Choosing the right piece of equipment is important for patient safety and also achieving therapeutic goals. Most retail equipment is designed for medium and large sized animals but can be modified or mimicked using different materials for smaller patients. For example, pole stepping equipment alternatives can include pool noodles cut in half, wooden dowels placed in a line or a coiled piece of garden hose. Pole stepping height can be raised by using cardboard boxes with holes cut at desired height or laundry hampers. Wobble boards can be made out of a lightweight piece of wood covered by non-slick mat material placed over a plastic bowel. The same platform can be angled to form a ramp. Cardboard boxes can be manipulated to form obstacle courses including pole stepping, crawling, pouncing or weaving depending on the desired exercise goals. If planned correctly, exercise equipment (common household items such as brooms and cardboard boxes) can be placed in an obstacle course pattern to encourage joint range of motion and proprioception in areas where the patient tends to travel. Alternatively, a designated area in the home can be set up with exercise equipment, preferably in a high traffic area. This method helps eliminate additional set-up or break-down time in addition to a visual reminder for the owner to encourage the pet to exercise. Motivators such as laser lights, toys, feathers or another pet can be utilized to further encourage participation in exercise. A short pick list of therapeutic exercise types is important to offer because not every exercise suits every patient (and owner). Exercise routines should vary to prevent boredom and muscle accommodation, with no more than 2 exercises chosen to be performed for a given therapy session and the home environment should be modified to accommodate any disabilities. In cats with debilitating osteoarthritis, modifications to the home environment should be made in the form of ramps, stairs or ledges in order for them to continue using their favorite resting spots (Epstein ME. 2015). Owner education and training must be performed by the veterinary team to ensure success and must include both verbal and visual demonstrations, with the owner repeating the exercise.

Clinicians and pet owners can provide an enriching environment coupled with fitness, coordination and strength exercise including the following:

- Land treadmill walking: active assistance for movement of painful joints, some cushion on impact, improves stifle extension, increases the stance time of limbs and encourages mild conditioning.

- Sit-to-stand: strengthen the hip and stifle extensors without causing extension of the hip, stifle, and hock and improves range of motion. Strength of the quadriceps, hamstring, and gastrocnemius muscle groups are targeted.
- Ramp or stair walking: improve powers in pelvic limb extensors.
- Cavaletti or pole walking: increases stride length, stance time, active flexion of the limbs and proprioceptive awareness. Height can be raised gradually, and poles space varied to increase difficulty.
- Pole weaving: encourages active lateral flexion of the spine, proprioceptive training, weight shifting, flexion/extension of the limbs, and conditioning of adductor and abductor muscles.
- Balance Boards, physiorolls and therapy peanuts: focus on proprioceptive development, activation of hip and shoulder stabilizers and activate core musculatures.
- Stations or combo courses: Combining exercises allows the patient to perform self-guided activity through targeted obstacles or courses. Commando crawling under objects, using elastic bands, controlled ball playing, walking backwards by retrieving a toy in a corner, platform courses, reaching for a laser light on the wall and jumping on low platforms.

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Lights, Camera, Action: Using & Understanding Therapeutic Laser for Pain Management

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Therapeutic Laser in Veterinary Medicine

Therapeutic laser has been a popular modality throughout human history since the 1960s when low powered lasers (<500mW, <35J/cm^2, typical wavelengths of 600-1300nm) were developed to manage pain, wounds and soft tissue injuries (Baxter 2002). As like most medical professions, veterinary medicine evolved where veterinarians and veterinary technicians alike are pursuing areas of specialization with board certifications in various specialty disciplines. From this, healthcare teams providing general medicine services can benefit from focused areas of research and innovation. Veterinarians boarded in a specialty often focus areas of interest in research and advancing the art of the specialty which provides increased access to valuable information for veterinary patients. Of particular growing interest for all practitioners, especially in the area of pain management, is photobiomodulation (PBM) or more commonly called therapeutic laser. This therapeutic modality is an effective adjunctive tool for pain management when used as part of a multi-modal pain treatment plan, is easily implemented in a clinical setting, provides short patient treatment times, and is readily accessible for veterinary practices of all types. With such widespread availability and increased awareness of the modality, some professionals are unfortunately discovering implementation of this therapeutic treatment does not adequately meet appropriate levels of understanding surrounding the mechanism of action, possible indications, precautions, effective treatment delivery methods to the animal and safety measures for personnel delivering the therapy leaving potential for perceived failed effectiveness claims and injury to the patient. Team members should become familiar with the aforementioned which ultimately leads to more comprehensive care for patients.

Photobiomodulation

Understanding laser classes and physics behind the science is the first step to successful implementation and communication with clients or colleagues. When used for rehabilitative purposes, lasers have been known as *low-level lasers*, *cold lasers or therapeutic lasers* and do not have power capable of thermal destruction of cells and tissues. In physical rehabilitation the term *therapeutic laser* is most appropriate for casual discussions while PBM should be used for scientific discussions. Photobiomodulation alters cellular function by modulating a process known as photobiostimulation and is defined as a non-thermal interaction of monochromatic radiation source within a target site (Millis DL. 2015), stimulating cellular mechanisms like mitochondrial respiration and adenosine triphosphate (ATP) synthesis to accelerate healing or regeneration.

Equipment Safety Classification

Therapeutic lasers are classified by the Food and Drug Enforcement Agency (FDA) on their level of safety and ability to cause injury to tissues, especially the eye, through thermal damage. Four safety classes are recognized by the FDA which are determined by power output in watts (W) and wavelength (λ) in nanometers (nm). Class 1 (supermarket scanners) and Class 2 (laser pointers) lasers are in the visible light spectrum between 400-700nm, are limited to 1 mW continuous wave and have very low energy or ability to damage the eye unless focused with a lens. Class 3 lasers include the therapeutic lasers causing modulation of tissue metabolism and can be further divided into 3a and 3b categories. They can be continuous or pulsed wavelengths with power ranging from 500mW to 30mW. Class 3a lasers emit visible light while Class 3b lasers emit non-visible light at the wavelength range where therapeutic effects are observed. Class 4 lasers require specific safety considerations, and depending on the output power, may be therapeutic (1 to 15 W) or surgical (30 to 100 W) lasers. The potential for beam reflection by both classes 3 and 4 lasers is high and individuals in the vicinity of treatments should wear personal protective eye equipment specific for the wavelength being used.

Physical Properties

Light Amplification by Stimulated Emission of Radiation (LASER) is monochromatic (one wavelength for increased absorption), coherent (photons travel in the same phase and direction for precise delivery) and collimated (little divergence in the beam over a distance). A laser is made using a material that then stimulated by an external energy source, such as electricity, will release photons of a certain wavelength (Shaw KK. Brown L. 2018). These properties of therapeutic lasers separate them from other forms of light and are responsible for little to no heating of tissues and therapeutic effects on chromophore absorption. The laser light interacts with tissues, especially the epidermis, by being reflected, scattered, transmitted or absorbed. Different types of lasers are available for medical or therapeutic use and differ in maximum power output, measured in watts (W). Laser units used for therapeutic use includes a Helium-Neon (HeNe) gas tube red light emitter, Gallium Arsenate (GaAa) or Gallium Aluminum Arsenate (GaAlAs) diode infrared light emitters. The HeNe gas tube produces wavelengths in the 632nm to 650nm range and may penetrate tissues 0.8mm to 15mm deep. GaAs and GaAlAs diodes produce wavelengths in the 820nm to 904nm

range and may penetrate tissues 10mm to 5cm deep, with direct effects up to 2cm in depth. All lasers emit tiny packets of energy called photons that exist with us in everyday life in the form of ordinary light from the sun, x-ray machines, light bulbs, laser pointers and microwave ovens. Photons move in wave-like patterns of specific length (e.g. wavelength) depending on the amount of energy they carry. On the electromagnetic spectrum, wavelengths may be very short (Gamma Rays, 0.01nm) or very long (radio waves – 1m) with visible (400-800nm) and infrared light (10μm) near the middle of the spectrum. Therapeutic laser wavelengths fall between the infrared or near infrared portion of the electromagnetic spectrum at 600-1200nm. Wavelengths in the near infrared ranges (e.g. shorter wavelengths) penetrate tissues the deepest of all waves in the visible spectrum, making treatment of deep tissues, trigger points, ligaments, joint capsules, and intra-articular structures possible while longer wavelengths closer to the visible spectrum stimulate superficial tissues and are best suited for acupuncture point stimulation or wound healing.

Cellular Response

Photon energy is absorbed by chromophores on cytochrome c oxidase within mitochondria and in cell membranes to produce a physiologic and metabolic response. Absorption of light in the red and near infrared ranges causes intracellular photochemical changes resulting in a downstream cascade of intracellular, extracellular and physiological effects such as the formation of proton gradients, stimulation of ATP and DNA production as well as increasing cell membrane permeability. Increases in cell metabolic rate results in faster production of material the cell manufacturers, for example chondrocytes producing more cartilage matrix. Low concentrations of reactive oxygen species (ROSs) are generated during the absorption of laser energy, leading to modulated cell metabolism, signaling and nitric oxide (NO) mobilization via photo-dissociation; leading to increased circulation and changes in inflammatory signaling (Gaynor J. 2015) having dramatic effects on granulating wounds and contaminated/infected areas. (Prydie D. 2015).

Application of Photobiomodulation

Dosage Considerations

Laser power, measured in a unit of time expressed in watts (W) or milliwatts (mW), and is emitted from a laser aperture. Power determines the dose or energy density and is measured by the number of Joules (J) delivered per surface area, measured in cm^2 (1 W = 1 J/sec), to tissues. Calculation of time is required for treatment delivery and can only be determined if output power of the laser and desired total dose for the condition are known. For example, to provide 1 J of energy density from a 500mW laser, the probe aperture would need to be held in one spot for 2 seconds to deliver 1 J of energy density. (e.g. 1 J = 1 W/sec; 500 mW = 0.5 W; 1 W/ 0.5 W = 2 seconds) (Millis DL. 2015). For most conditions, 1 to 15 J of energy density is needed for treatment with results being possible in 2 to 4 sessions for acute pain and 1 to 7 sessions for chronic pain. Other sources (Gaynor J. 2015) recommend 2 to 6 J/cm2 for superficial conditions and 6 to 10 J/cm2 for deep conditions like arthritis and tendon injury. Treatment times for energy density dosages change in relation to the laser power output capabilities. It should be noted that optimal energy density treatment time delivery needs further investigation and it is unknown if shortening the treatment delivery time by increasing power (Class 4) produces the same desired clinical results as longer treatment times (Class 3). Therefore, when increasing power or using different classes of therapeutic lasers, we cannot assume equivalent clinical results. Of additional debate is pulsing frequency, expressed in Hertz (Hz) of light energy. Therapeutic lasers possess the ability of turn emissions on and off at desired intervals and theory suggests that synchronizing aspects of pulsing frequency with biologic reactions optimizes treatments, however there is no agreement in the literature regarding optimal pulsing parameters for specific conditions and continuous wave treatment remains the gold standard for efficacy (Gaynor J. 2015).

Treatment Technique and Patient Preparation

Reflection of laser light may be reduced by using proper application technique, or beam direction, for the laser being used. Class 3 lasers typically employ a direct contact and point-to-point technique with little reflection risk to personnel but still require correct handpiece position for accurate delivery of energy into tissues. On contact point-to-point treatment a standard convex optic is used, and the handpiece is held in one location for the duration of the treatment. The handpiece may be held with light pressure on tissues or with slight increased pressure angled towards the target area. As pressure is applied the tissues are compressed, interstitial fluid is displaced, and penetration depth is increased slightly. Users should be aware of pressure application to treatment areas due to the stimulation of mechanoreceptors which may increase pain responses. Some patients may respond to increased pressure alone versus energy density delivered. If an animal begins to respond to treatment prior to its completion, the prescribing practitioner should be notified as this can be an indirect assessment of the current pain state and the energy density may need to be adjusted. When handpiece pressure is released from the target tissue and moved to a secondary location venous return normalizes. Treatment areas should be mapped out by users to ensure all locations receive the proper energy density, either over- or under- dosing. Direct point treatments should slightly overlap handpiece treatment surface area locations in a grid pattern. This application method is not indicated for open wounds, contusions or bony prominences. Class 4 lasers usually require a non-contact “scanning” method of delivery, but direct contact technique may be possible depending on the laser manufacturer specifications. Non-

contact or scanning methods can greatly affect beam reflection depending on how the hand piece is positioned during treatment. In most cases of non-contact method application, the best strategy for reducing laser light reflection is to hold the hand piece off the skin surface, directing the beam aperture as close to 90 degrees as possible to the target tissues (Millis DL. 2015). Off-contact techniques recommended by a manufacturer are also generally applied using diverging optics over a large area. The advantage to this treatment technique is being able to treat large areas and allowing users to vary the energy density of the treatment. This technique however increases variability of the energy density delivered when compared to a contact method and reflection of laser light increases at the tissue interface.

When applying therapeutic laser to animals, 50-99% of laser light can be absorbed by the hair. Shaving or trimming the hair should be considered, however in cases where this is undesirable the hair may be parted to expose the skin. It is not recommended to wet hair with water to gain access to the skin because nearly 100% of light is first absorbed by water and energy density delivery to tissues may be affected. The best location for treatment in the clinical setting is in a quiet room free of distraction and personnel traffic. It is very common for animals to fall asleep during treatment as natural endorphins are released into the circulatory system and pain levels are reduced. During treatment portions of the patient's body may need to be manipulated or supported. In most cases the probe aperture determines the angle a limb may need to be held or the position a patient lies down because the probe size in relation to the animal is difficult to position. For joints and muscles, new recommendations are being made to deliver therapeutic laser with the region in an open, stretched or extended position to maximize delivery to affected sections and mimic positions which may be incorporating additional areas causing pain. In very painful or fractious patients, the desired treatment area may need to be treated last to encourage building trust with the patient and to decrease pain levels. It is not uncommon in feline patients for a treatment to be interrupted due to poor patient compliance. In these instances, the patient should be allowed to reposition before resuming treatment. Treatments may need to be performed in the travel carrier with the upper portion removed or in the clients lap depending on the demeanor of the patient.

Patient Safety

Despite the wide safety margin, contraindications, precautions and considerations are used when applying therapeutic laser to certain conditions. Therapeutic laser use is contraindicated over a pregnant uterus, open fontanels, tattoos, growth plates of skeletally immature animals, the gonads, malignant areas, directly into the cornea and in areas of hemorrhage. Precaution is taken in photosensitive areas of the skin, recently traumatized or injured tissues with mechanical hypersensitivity and areas treated with medications or solutions. Patients receiving laser post-operatively must have any remaining cleansing solutions removed from the skin to avoid laser light absorption by the aseptic solutions being intensified and becoming painful. Topical medications, especially corticosteroids or transdermal opioids, may produce negative systemic effects and should be removed from treatment areas several hours in advance to avoid complications. Depending on the therapeutic laser power output, patients with dark skin or fur may need the laser aperture moved more frequently, especially with the point-to-point method, to reduce the melanin in pigmented areas quickly absorbing laser light, causing indirect heating effects. Normal tissues do not absorb laser energy and experience activation of PBM effects. In injured tissues, providing too much energy density to an area can have deleterious effects. The Ardnt-Shultz law describes weak stimulus as accelerating physiologic activity, medium stimuli inhibiting physiologic activity and strong stimuli possibly halting desired physiologic activity. On occasion, patients may experience extreme tiredness from the systemic release of metabolites and easing of long-standing pain. For example, trotting horses receiving therapeutic laser were completely sedated for two days after treatment but went back to competing as usual once recovered. In rare instances, patients may experience a pain reaction and is most commonly associated in the treatment of chronic conditions. Although the direct mechanism is undefined, the pain reaction causes the injury or condition to be made "acute" as the process of healing has been restarted after energy delivery to target tissues but is temporary. Another possible side effect from therapeutic laser treatment is a false picture of health. Patient pain can disappear very quickly but then become reinjured from overexertion or increased activity, giving owners the impression treatment was ineffective. To avoid this scenario, owner's must be reminded to follow exercise restriction guidelines during healing and reparative phases to avoid overloading damaged tissues.

Treatment Plan Delivery

Therapeutic laser is often used as an adjunctive therapy in the management of chronic pain conditions like osteoarthritis but it may also be used for musculoskeletal, tendon, or ligament injury, reduction of scar tissue formation, treatment of myofascial trigger points, stimulation or sedation of acupuncture points, improvement of chronic or acute skin wound healing times, reduction of localized bacterial counts, improved vascular and lymphatic flow, stimulation of nerve regeneration, and pain management. In summary, if a condition ends with an "–it is", it may potentially benefit from therapeutic laser.

Clinical Applications

The basis of any treatment plan relies on clinical examination and diagnosis by a prescribing veterinarian. Therapeutic laser energy density, or dose, is prescribed just as any other pharmaceutical, including treatment locations. It is imperative for a veterinarian team member to be assigned as the "laser expert", with additional team members possessing adequate knowledge and skill performing the directed treatment. Depending on the animal and veterinary practice, location in the practice for treatment varies. Some practices prefer to have patients dropped off for short periods of time because space is limited and using an examination room can be logistically difficult. Others may dedicate space for treatments, including comfortable accommodations for the patient, owner and personnel. During treatment delivery, patient behavior and response must be assessed. The behavior of an animal may indicate pain or stress and noting reactions to any one particular location point of treatment, muscular twitching, sensitive touch gradients or re-positioning of the animal, during treatment are important evaluation parameters. Ergonomic positioning for personnel is also essential to consider because patient positioning can be tricky. The patient should be as relaxed as possible and comfortable in the environment. Utilization of equipment such as tables, positioning aides and enticing food lures to keep the patient occupied help improve delivery of the treatment and reduce ergonomic stress to personnel. Some patients are simply fidgety and will not lie still while others are reluctant to move. When necessary, more than one team member in addition to the pet owner may be beneficial.

Medical Conditions

Knowledge of common conditions treated with therapeutic laser is important when veterinarians are deciding which patients may benefit from the modality. Therapeutic laser has long been used for wound healing and has the most profound evidence visually of healing. Other conditions can be more difficult to conceptualize because they rely on clinical improvement including: pain, inflammation, edema, osteoarthritis, intervertebral disc disease, referred back pain from visceral pain, post-surgical pain, myofascial trigger points, lick granulomas, neuritis, vestibular syndrome (secondary effects of), dental disease, dermal bacterial infections and muscle, tendon, ligament injuries. The easiest clinical application is for surgical conditions. Treatment sessions are easily built into the surgical estimate and patients are already present for the procedure and will need to return for follow up examinations to assess surgical healing. In some instances, therapeutic laser can be used for palliative care or in regions typically contraindicated for treatment, such as in cases where pain management supersedes risk of making the actual condition worse.

As previously discussed, and more commonly accepted, normal cells do not respond to laser light however evidence is growing to suggest otherwise. Photobiomodulation effects are retained in tissues for a time period, then released when "injury" occurs. Muscles rely heavily on ATP, the biological source of energy needed for muscle work and with pre-treatments may exhibit enhanced responses when injury occurs. The use of PBM to prevent muscle damage was first demonstrated in animal models by irradiating tissues prior to intense exercise then measuring creatine kinase levels in the bloodstream. The study by Lopes-Martins et al. in rats assessed the effects of therapeutic laser at varying doses and the reduction in muscle fatigue and muscle damage (CK) induced by neuromuscular electrical stimulation. The study reported a dose response with the energy density (J/cm^2) and its ability to decrease CK levels. While more studies are needed to determine optimal dosages and timeframes prior to tissue injury, some practitioners are recommending the pre-treatment of areas designated for surgical intervention to enhance the modulatory effects of light energy. When using PBM as a post-operative pain management tool, the following considerations are evaluated:

- PBM is performed after cryotherapy, which causes vasocontraction thereby maximizing absorption by the target tissue (Dragone L. et al. 2015)
- Wounds or probe apertures should be covered by a clear plastic wrap fitted tightly to avoid reflection of light energy and contamination of the wound.
- Tissues must not be actively bleeding.
- A grid technique is used for delivery of treatment (e.g. a screen can be imagined over the wound in squares) with care taken to not overlap grid sections and overdose the treatment area.

Energy Density Guidelines – "Dosage"

Protocols for wound care based on the World Association of Laser Therapy (WALT) recommend acute open wounds to be treated in a non-contact method with 2-6 J/cm^2 SID for 7-10 days and 2-8 J/cm^2 SID chronic open wounds. Post-surgical wounds may respond well to a daily dose of 1-3 J/cm^2 for the first 7-10 days followed by a 1- to 2-day break, continued until the wound is healed. Often high interval treatment schedules are difficult for owners to adhere to, therefore treatment three times a week may be performed.

Treatment with PBM is a non-invasive way to provide pain relief when pharmaceutical medications are unable to be used in the treatment of chronic conditions such as osteoarthritis. Osteoarthritis affects a large number of animals with 100% of cats over the age of 10 being affected and often patients suffer from comorbidities or physiology preventing regular use of pharmaceutical medications. Therapeutic laser may help reduce the overall need for

pharmaceutical intervention over time and has anti-inflammatory properties similar to nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids. Anti-inflammatory effects through inhibition of the cyclooxygenase-2 (COX-2) enzyme and prostaglandin E_2 (PGE_2) production have been studied in cell culture (Honmura A. 1993), animal models (Sakurai Y. 2000), and people with Achilles tendinitis (Medrado AR. 2003). Treatment with PMB should occur in conjunction with a multimodal approach of pain management and not be viewed as a stand-alone therapy. Dosages range between 6 to 12 joules/cm^2 for chronic conditions and are directed at affected joints as well as secondary and tertiary compensatory areas. Treatments may be performed two to three times per week and then gradually reduced to once a week, and then if possible, every few weeks to manage long term pain.

Soft tissue injuries encompass muscles, tendons and ligaments and have prolonged recovery times. Ligaments extend between bones to stabilize joints, whereas tendons permit movement of bones by connecting muscles to bones. Both are pliant and flexible to allow movements but can become easily damaged during activity and heal very slowly due to poor vascularization and reduction of tensile strength. Similar to osteoarthritis, the affected region and any compensatory areas including the length of the superficial aspect of the tendon should be treated to help relieve arteriolar muscle spasm, excite electrons in the mitochondrial membrane to induce changes in cellular metabolism, and depolarize abnormally contracted muscle fibers with regions of localized ischemia. For example, the biceps tendon communicates with the shoulder joint capsule; therefore, the shoulder joint capsule should be treated as well. In some animals, pain may be referred to the cervical spine necessitating treatment. The therapeutic dose for muscle is 5-7 joules/ cm^2 and tendons 7-8 joules/ cm^2 with treatments occurring twice weekly for 4 to 6 weeks before reassessment occurs.

Devastating injury occurs when a patient suffers from neurological injury through paralysis, loss of independence and development of compensatory movements when relative functional movement returns. In one study, the use of therapeutic laser on peripheral nerve regeneration was evaluated after a crushing injury and showed that laser therapy was effective in promoting nerve recovery and axonal sprouting. Another study investigated the effect of laser therapy applied directly to areas with nerve injury and corresponding segments, demonstrating outcome improvements in overall function (Millis DL. 2015). It is important to note that these studies were performed immediately following injury but in some human patients with nerve injuries of more than 6 months duration, therapeutic laser resulted in progressive improvement of peripheral nerve function (Rochkind S. 2004). Treatment frequency for acute post-operative neurological conditions should occur daily as long as the patient is hospitalized. Chronic spinal cord conditions should initially be treated 2 to 3 times weekly for 4 to 6 weeks or as long as needed based on recovery. Therapeutic energy doses for acute conditions range between 2-4 joules/cm^2 while chronic conditions may benefit from 4-6 joules/cm^2. Treatment locations should include the injury location itself, two spinal cord segments above and below the injury, paraspinal musculatures and any tertiary areas of compensation (Gross D. 2014).

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Feline Hypertension: New Developments on a Pressing Topic

Bianca Lourenço, DVM, MSc, PhD, DACVIM (SAIM)

Introduction

Insidious in nature, systemic arterial hypertension has commonly been referred to as a 'silent killer'. Despite its potential impact in our patients' quality of life, hypertension remains an underdiagnosed condition as blood pressure (BP) measurement is not routinely performed across small animal practices.

Causes of hypertension in cats

In contrast to what is observed in human beings, feline hypertension is most often secondary to systemic diseases, such as chronic or acute kidney disease, hyperthyroidism, or the less frequently diagnosed hyperaldosteronism, hyperadrenocorticism and pheochromocytoma. In a subset of cats, no identifiable cause is found and a diagnosis of idiopathic hypertension is made.[1]

In addition to these causes of "true" pathologic hypertension, BP may be elevated due to stress or anxiety ('white-coat hypertension', now termed 'situational hypertension').[2,3]

Prevalence

Systemic hypertension is frequently present in association with diseases that typically affect older cats. It is estimated that significant elevation of BP occurs in **20-65% of cats with chronic kidney disease** (CKD) and **up to 87% of cats with hyperthyroidism**.[3] Hypertension can also be detected in nearly half of the cats presenting with acute kidney injury, and may not resolve as cats recover from this condition.[4]

Clinical significance

While hypertension is most often occult, persistent and/or severe systemic hypertension can lead to **damage** of four so-called "**target organs**":

- kidneys: progression of kidney disease and proteinuria;
- eyes: retinopathy/choroidopathy;
- brain: encephalopathy, stroke;
- heart: left ventricular hypertrophy.

Retinal detachment is perhaps one the most acutely and immediately impactful consequence of severely elevated systemic blood pressure; however, subclinical changes to those four organs are other significant concerns. The link between systemic hypertension and proteinuria is of particular relevance, as the latter is strongly associated with survival in this species.[5]

Diagnosis

Measurement of blood pressure

The Doppler and oscillometric methods are frequently used for noninvasive, indirect estimation of blood pressure in clinical practice. When operated by a trained individual, the Doppler is a faster and more reliable choice for blood pressure measurement in conscious cats.[6,7] More recently, high-definition oscillometry has been developed and shown to have reasonable accuracy for determination of systolic blood pressure in healthy awake cats.[8]

Regardless of the choice of equipment, systolic blood pressure measurements can be significantly impacted by many other factors, such as the operator, size of the cuff, environment, the cat's position, body and muscle condition, and the site of measurement.[9,10]

The best **tools for improved confidence in the diagnosis** and better management of hypertension are:

1. To repeat evaluation of blood pressure using a consistent technique that minimizes stress for the cat;
2. To acquire multiple measurements in each session: 5 to 7 consistent measurements;
3. To assessment of trends rather than isolated values.

Blood pressure categories

Recently updated guidelines from the American College of Veterinary Internal Medicine define categories for risk of target organ damage (TOD) according to a sliding scale of systemic blood pressure elevation (Table 1).[3] These risk categories are helpful in guiding treatment decisions.

Table 1 - Systemic hypertension in both dogs and cats classified based on the risk of target-organ damage.

Systolic BP (mmHg)	Updated Category	Risk of Target Organ Damage
< 140	Normotensive	Minimal
140 - 159	Prehypertensive	Low
160 - 179	Hypertensive	Moderate
≥ 180	Severely hypertensive	High

Who should be screened?

- Cats presenting with evidence of TOD;
- Cats diagnosed with diseases known to be associated with secondary hypertension;
- Older cats, as systemic hypertension is often present in association with diseases that commonly affect this population.

Treatment

The goal of antihypertensive therapy is to prevent TOD. Hypertension may be appropriately treated, and TOD may be prevented, using medications such as the calcium channel blocker, amlodipine, or the angiotensin receptor blocker, telmisartan.

The first steps in deciding whether hypertension warrants treatment are to document that BP elevation is a repeatable finding, and to investigate for possible target organ damage. Unless antihypertensive therapy is considered an emergency (i.e., presence of retinal detachment, hypertensive encephalopathy, or stroke), it is best to repeat the measurement at a follow-up office visit or, perhaps even better, a home visit.

When should treatment be initiated?

- Treatment is recommended for cats with systolic BP consistently in the hypertensive range (≥160 mm Hg) and those with evidence of TOD.
- Diagnostic investigation should be conducted so that an inciting cause for hypertension (e.g., renal disease, hyperthyroidism) is identified.
- Management of the primary disease should be concurrent with antihypertensive medication, as BP reduction may not occur by treating the inciting cause alone.

Calcium channel blockers

- Amlodipine is a first-line therapy.[3,11]
- It is efficacious, inexpensive and only requires once-daily dosing.

Renin-angiotensin-aldosterone system (RAAS) antagonists

- The angiotensin receptor blocker, telmisartan, is the first in its class to be FDA-approved for the control of systemic hypertension in cats.
- RAAS antagonists should not be used in dehydrated cats.

Monitoring

- Treatment should target a systolic BP <160 mmHg or optimally <140 mmHg.[3]
- BP should be measured 7 to 10 days after antihypertensive therapy is initiated, or there is a dose change.
- Dosing instructions of antihypertensive medication should be followed to achieve targeted BP values, and dosage should be appropriately decreased if there is evidence of hypotension.
- In some cases, combination therapy is required, and alternative antihypertensive medications are added to the initial treatment.
- When target BP is achieved, cats should be monitored every 4 to 6 months. Recheck visits should include BP measurement, fundic examination and periodic monitoring for ongoing or newly developed renal, cardiac or neurologic disease.

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Artificial Intelligence Takes the Surprise Out of Chronic Kidney Disease

Dennis Chew, DVM, DACVIM

Chronic kidney disease (CKD) is characterized by the development of intrarenal lesions that are irreversible and variably progressive.[1,2] These lesions are clinically associated with decreased GFR, loss of renal excretory ability, decreased ability to conserve electrolytes and proteins, reduced ability to maximally concentrate urine, and decreased ability to synthesize calcitriol and erythropoietin depending on how advanced the disease has become. The definition of "chronic" requires documentation of an ongoing intrarenal process from 1 to 3 months.

The frequency for the diagnosis of CKD is more common in cats compared to dogs, especially in geriatric cats. Azotemic CKD was diagnosed in 8 to 31% of geriatric cats in several studies.[3-6] The prevalence for a highly likely diagnosis of CKD for cats in primary care practices was 17%, and increased to 42% when a probable diagnosis of CKD was considered.[7] When CKD included IRIS stage 1 and stage 2 cats, the prevalence of CKD in random source control cats of various ages was detected in 50% and in 68.8% of cats that also had a diagnosis of degenerative joint disease.[5] In one study, CKD was the leading cause for mortality in cats ≥ 5 years of age and the number two cause of death in cats of all ages examined at primary care practices.[8]

The initial clinical diagnosis of CKD is made on some combination of findings from owner reported clinical signs, physical examination (especially large or small kidneys, irregular kidneys, hard kidneys), systemic blood pressure, renal imaging, urinalysis, urine biochemistry (UPC), and serum biochemistry (BUN, creatinine, phosphorus, SDMA). A specific diagnosis for the underlying CKD is often not possible and many are diagnosed with "idiopathic" chronic interstitial nephritis. Tubulo-interstitial nephritis of unknown origin is the most common cause of azotemic CKD in the cat, as in the dog. Glomerulonephritis as the cause for CKD is less common in cats than in dogs. Cats have several renal diseases that deserve additional consideration, including breed-related predilection for renal amyloidosis (Abyssinian, Oriental Short Hair) and polycystic kidney disease (Persian, Himalayan). Cats also have greater frequency of CKD associated with renal LSA than dogs. Peri-nephric pseudocyst can be associated with CKD in cats and should be considered as a differential diagnosis for apparent renal enlargement in addition to renal LSA and hydronephrosis.

Prediction of a CKD Diagnosis

An increased risk for the diagnosis of CKD was shown for cats that had thin body condition, a diagnosis of periodontal disease or cystitis, had undergone anesthesia, or were noted to have dehydration in the preceding year. Neutered male cats were at increased risk compared to spayed females for CKD in the same study.[9] Periodontal disease was associated with increased risk for a future diagnosis of CKD, with the greatest risk for cats with stage 3 or 4 periodontal disease. Anesthesia or a diagnosis of cystitis within the past year were also risk factors for a diagnosis of CKD to emerge.[10]

An early study using multivariable analysis showed that serum creatinine in combination with renal proteinuria (UPC or UAC) predicted the onset of azotemic CKD in client-owned cats within one year. However, the sensitivity and specificity for this prediction was not sufficiently high for routine use in clinical practice. USG was lower at the start of the study for cats that developed azotemia within one year compared to those that did not do so. At 12 months, USG decreased in both groups, but more so in cats that developed azotemia. USG was significant in the univariable but not the multivariable analysis.[11]

Concentrations of the phosphatonin FGF-23 (fibroblast growth factor-23) predicted which healthy geriatric cats would develop azotemia within 12 months in one study. Cats with the lowest FGF-23 concentrations did not develop azotemia during this time, whereas cats with intermediate or high levels of FGF-23 emerged with either a serum creatinine of 1.6 to 2.0 mg/dL or > 2.0 mg/dL respectively.[12] FGF-23 is not yet available as a biochemical test that can be ordered from commercial veterinary laboratories.

The power of artificial intelligence and machine learning was harnessed to develop a proprietary renal diagnostic index (RenalTech™; Antech Diagnostics and Imaging) that was launched in the last half of 2019. This index generates a prediction whether CKD in cats will develop over the next two years. Large data sets from many primary care practices using the same analyzers and electronic medical record system were used to develop and then test the predictive model in cats. BUN, serum creatinine, USG, and age engage the algorithm over different time points for analysis from within the laboratory data system. These 4 parameters were determined to be the most useful and accurate parameters to predict a future diagnosis of CKD from an initial 35 that were evaluated. This index performed well for accuracy (hybrid of sensitivity and specificity), sensitivity (ability to identify those with a future diagnosis of CKD), and specificity (ability to identify those that will not achieve a diagnosis of CKD) in a recent report. This diagnostic index identified

63% of cats that developed a diagnosis of CKD 1 year before the diagnosis and 44% of cats 2 years before the diagnosis. The ability to identify cats that did not develop CKD over the next 2 years remained over 99%.[7]

This renal diagnostic index has been further developed to add dipstick values for urine protein and pH as well as the total white blood cell count in blood to the cascade of algorithms depending on results of the initial 4 parameters. The addition of these 3 parameters can improve accuracy for the prediction of a future CKD diagnosis at times; the algorithm makes the decision to use only the initial 4 parameters or to add the other 3 as needed. The algorithm can work to analyze data from a single time point, but performance of the prediction improves when multiple time points for data evaluation are used for analysis. The prediction also works better when all the data points are available for evaluation. Accuracy of the prediction is better when USG is entered into the calculations, but a USG can be imputed if there is no USG available for a particular visit. Laboratory data fed into the algorithm should be generated from the same analyzers (all reference lab or all in-house analyzers, not a mixture of results from different analyzers) in order to improve the prediction accuracy. A score is generated between 0 and 100 with low scores predicting cats that are not likely to develop CKD within 2 years and high scores predicting cats that are likely to develop CKD within 2 years. Most cats fall into the category of either not likely or highly likely to develop CKD within the next 2 years. This algorithm is able to identify subtle changes and trends in data that may not be obvious to the primary attending veterinarian. The generated score is intended to provide a reminder to the attending veterinarian about the likelihood of a CKD diagnosis to emerge over the next two years. This likelihood could then inform decisions to provide more detailed client education, recommendations for other diagnostics (UPC, blood pressure) and implementation of treatment (diet, drugs), if any is indicated. An advantage for the use of this renal index is that routinely measured parameters in the medical record are available for analysis and scoring by the algorithm. Ongoing studies are needed to determine if this renal index can predict the emergence of CKD by IRIS stage and how this index compares with prediction of a future diagnosis of CKD based on various combinations of FGF-23, UPC, and USG.

Progression of CKD

Progression of CKD refers to ongoing loss of functional renal mass and accumulation of primary chronic renal lesions (tubulo-interstitial nephritis, fibrosis, and nephron drop-out) associated with decreasing GFR.[1,2] When enough loss of nephron mass occurs, increases in BUN, creatinine, SDMA, and phosphorus will be detected in serum biochemistry. Progressive loss of excretory renal function and ability to concentrate urine will occur if the cause of the initial renal injury is not detected and stopped early, as can occur with various types of immune-complex glomerulonephritis, familial glomerular disease, and renal amyloidosis. The “inexorable progression” of CKD occurs after a substantial amount of renal mass has already occurred. This type of progression can continue even when the original cause of the renal injury has been stopped. Based on experimental data, this type of self-progressive destruction of the kidney likely occurs in cats when there is loss of at least 75% of the original renal mass. Glomerular hyperfiltration and glomerular hypertension are considered to be important players that exist in the surviving single nephrons in advanced CKD that contribute to this type of progression. Systemic hypertension, PTH, CKD- BMD (bone mineral disease associated with phosphorus, FGF-23, Klotho, ionized calcium) and oxidative stress are also likely to contribute to progression.

CKD is variably progressive in cats with azotemia, though some cats appear stable for long periods of time (physical exam and laboratory parameters). The rate of progression must be determined for each individual cat over time. An increase in serum creatinine of ≥ 25% over baseline during the next 12 months was observed in 47% of cats with newly diagnosed azotemic CKD (serum creatinine > 2.0 and UG < 1.035) in one study. Many cats of this study had slowly progressive or nonprogressive CKD when assessed by IRIS stage. Thirty-three percent of cats initially diagnosed in IRIS stage 2 did not advance to a higher stage during the year of this study. Very few cats initially diagnosed in IRIS stage 2 advanced to IRIS stage 4 by the end of the study whereas 62% of the cats initially diagnosed in IRIS stage 2 advanced to IRIS stage 3 within 12 months.[13] About 31% of apparently healthy geriatric cats developed azotemia within 12 months of an earlier study.[11] It is not known how many cats initially diagnosed with IRIS stage1 CKD will progress to IRIS stage 2 or higher.

Risk Factors for Progression of CKD

Serum creatinine at the time of CKD diagnosis predicted survival in cats with CKD in most studies[14-17] but not in one.[18] Phosphorus retention in the body is a well-known risk factor for progression of CKD in cats based on accumulation of renal lesions, loss of excretory function, and decreased survival time.[14,19-25] In one study, an increase of serum phosphorus of 1 mg/dL increased the risk of progression by 43% within one year.[13] Serum phosphorus was the only variable predictive of survival of CKD cats in another study; the risk for death increased by 11.8% for each increase in serum phosphorus of 1 mg/dL.[14] Cats with serum phosphorus < 4.7 mg/dL at the time of CKD diagnosis lived longer than CKD cats with higher values.[16] CKD cats that maintained a serum phosphorus < 4.5 mg/dL lived considerably longer than cats with higher values in one study.[25] Phosphorus retention within the body occurs during CKD even when serum phosphorus is still within the reference range, as suggested by increased concentrations of PTH and FGF-23.[17,19,26]

Sometimes the calcium x phosphorus product (CPP) reveals abnormalities when neither the calcium nor phosphorus alone do so; this concept is less well studied in cats than in dogs. In one study of CKD cats, a higher CPP was associated with progression.[27] CPP was related to magnitude of increased serum creatinine cats with CKD and was higher in cats with gastric mineralization.[28]

CPP has been positively associated with FGF-23 concentrations.[12] Increased FGF-23 at diagnosis was an independent predictor of survival time and progression of CKD within the next 12 months, along with plasma creatinine, UPC, and age. The highest levels of FGF-23 were associated with a 4 times increased risk of death. It is unknown if FGF-23 is solely a marker of CKD or if it can also directly create renal injury.[17]

Indoxyl sulfate (IS) is a uremic toxin that can serve as a biomarker to predict CKD progression. Levels of IS were significantly higher in cats that had progression of their CKD, both in IRIS stage 2 and 3. Progression was defined as an increase in IRIS renal stage or an increase in serum creatinine of ≥ 0.5 mg/dL within a 3-month period.[27] In another study of cats diagnosed with CKD and serum creatinine ≥ 1.6 mg/dL, higher levels of both IS and FGF-23 were associated with renal progression. Progression was defined as an increase of serum creatinine ≥ 0.5 mg/dL over baseline within 3 months. The combination of FGF-23 and IS predicted progression of CKD in these cats more precisely when used together rather than separately. Both IS and FGF-23 concentrations were highly correlated with phosphorus, indicating an intimate association of phosphate metabolism and CKD progression in this study.[29]

Proteinuria and Systemic Hypertension

Proteinuria as measured by UPC at the time of CKD diagnosis in cats predicted survival time and progression.[13,16,17,30] A high UPC predicted progression of all CKD cats in one study[13] and was found to be an independent risk factor for shorter survival times in another study.[16] A UPC of > 0.4 at the time of CKD diagnosis in cats was associated with the shortest survival time, intermediate survival was found for those with a UPC of 0.2 to 0.4 and the longest survival times were found in cats with a UPC < 0.2.[30] A UPC ≤ 0.2 had the longest survival and UPC > 1.0 the least survival in CKD cats of another study.[16] Small differences in UPC appear to have a large impact on the projected survival time in CKD cats.

Blood pressure was infrequently measured (1.3% of all cats examined and in 4.4% of cats ≥ 9 years of age) in one general practice primary care study. Blood pressure most commonly was measured in cats with clinical signs of illness, followed by cats under anesthesia, monitoring of pre-existing disease, monitoring of pre-existing hypertension, and very uncommonly during geriatric health visits. When blood pressure was measured, 19.5% (282 of 1445) were documented to have hypertension, and CKD was the most common co-morbidity (46.1%) at the time of hypertension diagnosis. Idiopathic hypertension accounted for 30.5% of hypertensive cats but many cats did not have extensive investigation for an underlying cause. Cats with CKD or diabetes mellitus and hypertension had increased risk for death in this study. Hypertensive cats that were screened for the development of hypertension lived longer than cats that had their hypertension discovered related to onset of clinical signs. Most cats with hypertension in this study had ≥ 180 mm Hg systolic blood pressure which provides severe risk for target organ damage. This study suggested that tighter control of blood pressure during treatment in hypertensive cats resulted in less morbidity from target organ damage.[31]

Up to 65% of cats with CKD evaluated at referral hospitals have systemic hypertension.[32,33] The prevalence of systolic hypertension was considerably lower at 19.4% when evaluated in cats in primary care practice.[34] The documentation of systemic hypertension was not associated with the magnitude of azotemia in two studies.[32,34] Plasma potassium concentrations were significantly lower in CKD cats that were documented to have hypertension in one study, but the magnitude of difference between that in the normotensive and the hypertensive group was small.[34] The prevalence of hypokalemia in azotemic cats is common and was about 30% in one report.[35] Systemic hypertension potentially increases progression of CKD as high systemic pressures are transmitted to the glomerulus which then increase the degree of glomerular hypertension in remnant nephrons. The increased glomerular pressure as well as an increase in transglomerular passage of plasma proteins can result in glomerulosclerosis and tubulo-interstitial inflammation which further reduces functional nephron mass.[36]

In cats with CKD, 105 of 265 (40%) were hypertensive at initial evaluation. Twenty-seven of the160 (16.8%) initially non-hypertensive CKD cats and 9 of the 133 (6.8%) healthy cats ≥ 9 years of age developed hypertension ≥ 3 months after the first visit. Systolic blood pressure increased with age in all cats and serum creatinine was an independent predictor for the development of new onset hypertension. Results from this study provide support for the recommendation to regularly monitor blood pressure in elderly cats, especially those with CKD.[37]

Studies of clinical cats with CKD have failed to show that systemic hypertension decreases survival, likely due to effective antihypertensive treatment that readily returns systemic blood pressure to normal. No studies include non-treated client-owned hypertensive cats as a control group, as withholding this treatment is unethical. Clinically relevant reduction in the magnitude of systemic hypertension is readily achieved with amlodipine in most CKD cats at 0.125

mg/kg to 0.25 mg/kg once daily by mouth.[38-41] Survival did not decrease in CKD cats that were hypertensive at the time of diagnosis following treatment that lowered systemic blood pressure. Systolic blood pressure along with creatinine was associated with the magnitude of proteinuria.[30] In another study of 141 client-owned cats with systolic hypertension treated with amlodipine, survival was only related to UPC and not the degree of blood pressure control achieved. The degree of proteinuria before and after treatment, was strongly associated with survival. The degree of proteinuria was greatest in cats in the upper quartile of blood pressure and lowest in cats in the lower quartile of blood pressure. Treatment with amlodipine resulted in a significant decrease in UPC in these CKD cats, an effect that was greater in cats with higher UPC before treatment. Amlodipine dosed at 0.625 mg/cat once daily provided effective control of blood pressure in 50% of hypertensive cats; the other 50% required a dose escalation to 1.25 mg/cat per day in the same study.[38] It seems paradoxical that proteinuria predicted survival of CKD cats and that blood pressure was related to the degree of proteinuria, yet blood pressure was not related to survival in two studies.[30,38]

Treatment of CKD with Renal Diets and Intestinal Phosphate Binders

Commercially available renal diets are lower in protein, calcium, phosphorus, and sodium content, and higher in potassium, alkali precursor (usually citrate), omega-3, and energy content, compared to diets designed for healthy cats. It is important to consider intake of nutrients on an energy density basis (mg or G per 100 or 1000 kcal) in order to compare diets. It is well established that diets formulated to treat renal disease confer benefits to CKD cats in IRIS stages 2 to 4. Benefits include both increased survival time and fewer episodes of a uremic crisis that would require hospitalization for treatment.[21,42,43] Since many nutrients are altered in these diets, it is not possible to identify an individual nutrient change that confers benefits. However, it appears that phosphorus restriction may be the single most important nutrient alteration.

There is some controversy regarding the use of renal diets for cats in IRIS CKD stages 2 to 4.[44,45] Protein restriction in renal diets can reduce lean body mass and quality of life due to protein:calorie malnutrition, especially in the earlier stages of CKD. The goal is to provide minimal protein restriction while maximizing the degree of phosphorus restriction. More severe restriction of dietary protein intake is generally indicated during advanced phases of CKD in which generation of uremic solutes and toxins might be lessened with lower protein intake. Adequate consumption of calories is always important, otherwise dietary proteins will be consumed as an energy source along with generation of more waste products that can accumulate in the circulation.

Phosphorus Control

Phosphorus content varies widely in commercially available foods. Renal diets are specifically formulated to reduce phosphorus content to limit total body phosphorus accumulation during CKD. Commercial foods can have phosphorus contents approaching 500 mg/100 kcal, whereas the average phosphorus content in feline renal diets is about 100 mg/100 kcal, slightly below the AAFCO minimum of 125 mg/100 kcal.[46] Normal histologic renal structure was better preserved in cats with CKD fed phosphorus-restricted diets compared to those fed higher levels of phosphorus.[20] Extended survival for CKD cats fed a renal diet was largely attributed to the degree of phosphorus and PTH control in one study.[21]

Targeted serum phosphorus control is recommended. IRIS (2019) recommends the chronic maintenance of serum phosphorus < 4.6 mg/dL and > 2.7 mg/dL in cats with CKD stages 2 to 4. The value for phosphorus-restricted diets has not been determined for IRIS stage 1. Alternatively, maintaining serum phosphorus in the lower half of the reference range is recommended to minimize adverse effects during CKD. It is more difficult to achieve targeted levels of serum phosphorus in cats that are eating more, eating a higher content phosphorus diet, eating diets that are high in inorganic phosphorus content, and cats that have poor renal excretory function associated with advanced CKD (higher IRIS stage). Serum phosphorus control requires a combination of feeding a phosphorus-restricted renal diet and the administration of intestinal phosphate-binding agents.

Intestinal phosphate binding compounds are based on salts of aluminum, calcium, lanthanum, iron, or sevelamer. Most doses of phosphate binders are 30 to 60 mg/kg/day divided into food, but higher doses may be needed to achieve the desired targeted level of serum phosphorus. The goal is for the binder in the food to bind with phosphate and be eliminated in the feces before being absorbed into the circulation. Binders that are not absorbed into the circulation are more desired so as to lessen potential toxicity. Lanthanum carbonate has been studied extensively in cats for safety and efficacy, and has been found to be an excellent phosphate binder with minimal to no recognized toxicity in cats.[22] Epakatin® (Vetoquinol) provides a combination of calcium carbonate and chitosan designed for phosphate binding; it is likely that calcium carbonate provides most of the binding. This product has demonstrated efficacy in decreasing serum phosphorus in cats with early clinical CKD that were eating regular maintenance diets.[47] Lower serum phosphorus and PTH resulted when this phosphate binder was added to a maintenance diet for cats with experimental CKD equivalent to IRIS stage 1 and 2.[48]

The first step in serum phosphorus control is to feed a phosphorus-restricted renal diet. If the targeted level of serum phosphate is not achieved with this diet, a different diet with a lower content of phosphate can be fed, or add an intestinal phosphate binder to the renal diet. Phosphate binders can be added to regular maintenance foods when CKD cats will not eat a renal diet, though this makes it more difficult to achieve the targeted serum phosphate level. Phosphate binders should be mixed into or adhere to the food; this is easier with wet foods. A concern is that binders added to food will inhibit food intake in cats, especially in cats that are azotemic.

In early stages of CKD, dietary phosphorus restriction alone can achieve the desired serum phosphorus concentration, but this is unlikely as CKD advances. Adding phosphate binders to maintenance diets of cats in early CKD can also be successful, but this is also unlikely to be effective in more advanced states of CKD. Doses of phosphate binders are sequentially increased as needed after evaluation of fasting serum phosphorus measured in about 4 weeks. Rarely, hypophosphatemia can occur; if this occurs the phosphate binder should be stopped and restarted at a lower dose. It is not always possible to achieve the targeted level of serum phosphorus despite the feeding of a renal diet and high doses of phosphate binders. Toxicity is a concern with administration of high doses of phosphate binders. Aluminum toxicity has not been specifically studied in cats with CKD, but it is of increasing concern in dogs with CKD.[49,50] Measurement of serum calcium should be sequentially evaluated in cats receiving calcium-containing phosphate binders to ensure that hypercalcemia does not develop. Lanthanum salts appear to be the most effective and safe phosphate binders for CKD cats, but this product is very expensive.[22] Iron salts for use in cats with CKD have been developed but not yet marketed.[51] Combination of different classes of intestinal phosphate binders may allow better phosphate control without increasing the chances for toxicity. In the future, the effectiveness of total body phosphate control will likely involve measurement of vitamin D metabolites, FGF-23, Klotho, and indoxyl sulfate in addition to the more commonly measured serum phosphorus and PTH.

Adverse Effects of Diets on Healthy Cats

There is renewed interest in dietary phosphorus content and effects on renal function in healthy cats.[52-55] Cats eventually diagnosed with CKD consumed significantly more protein and phosphate prior to a diagnosis of CKD compared to cats that did not develop CKD. This suggests a link between chronic consumption of high phosphate content diets as a possible cause of CKD in cats.[54]

Adverse effects on renal function occurred when high-phosphorus food (>5X maintenance requirements) was fed to normal cats for 29 days. Endogenous creatinine clearance decreased in cats fed the high phosphorus diet, indicating decreased excretory renal function. Glucosuria and microalbuminuria were only observed in cats consuming high-protein diets; they also showed considerably more phosphate excretion into urine.[53] Two levels of dietary phosphate (1.2 vs 4.8 g/1000 kcal) were studied in normal cats but was stopped prematurely after 4 weeks. Cats consuming high phosphorus showed a dramatic decrease in GFR and changes in renal ultrasonography. A study feeding lower dietary phosphorus (1.3 vs. 3.6 g/1000 kcal) for 28 weeks showed no changes in GFR, but altered renal echogenicity and nephrolithiasis was observed in 36% of cats consuming the higher phosphorus diet. A Ca:P ratio close to 1.0 resulted in less structural changes observed on ultrasonography. It was concluded that in cats, the no observed adverse effect level (NOEL) for dietary phosphorus is < 3.6 g/1000 kcal.[54]

Dietary phosphorus bioavailability is highly influenced by whether phosphorus is organic or inorganic. Organic sources of dietary phosphorus are generally less available. In cats, postprandial serum phosphorus concentrations increased to a much greater extent when inorganic dietary sources of phosphorus were utilized.[52,56] Higher phosphate urinary excretion is associated with higher renal tubular fluid phosphorus concentration which is potentially toxic to renal tubules (phosphatopathy) and may promote renal mineralization.[57-59]

Diets for CKD IRIS Stage 1

There is no evidence that diets or drugs can prevent the advancement of IRIS stage 1 cats to stages 2 to 4. IRIS stage 1 is the most difficult to assign with certainty in cats with serum creatinine < 1.6 mg/dL. Some cats with IRIS stage 1 either do not progress to higher stages, or progress very slowly. In these cats, IRIS stage 1 may indicate previous kidney damage and nephron mass loss that was minor and not currently progressive.

Healthy geriatric cats were fed a reduced protein and phosphate content food that was supplemented with some combination of fish oil, L-carnitine, and medium chained triglycerides. No changes attributed to diet were found for GFR, BUN, creatinine or SDMA over the six months of this study. Some cats likely had IRIS stage 1 CKD based on increased SDMA in combination with a reference range creatinine concentration.[60]

Client-owned cats ≥ 9 years old with serum creatinine within the reference range were fed a test food or owner-choice foods for 6 months. The test food was increased in content of fish oil, antioxidants, botanicals, amino acid supplements, and highly bioavailable protein. Cats consuming the test food decreased serum creatinine and BUN slightly while there was no change in cats consuming owner-choice foods. SDMA increased and USG decreased slightly in cats

consuming owner-choice food, and did not change in cats fed the test food. UPC did not change in either group. It was suggested that geriatric cats with IRIS stage 1 (reference range creatinine and increased SDMA) eating the test diet had greater stability of renal function compared to cats eating owner-choice foods. A limitation of this study was that GFR was not measured as the gold standard for excretory renal function and renal mass.[61] Longer studies are needed to determine if any of these cats had progressive chronic kidney disease severe enough to escalate to IRIS stage 2.

Two commercial renal diets (Diet A Royal Canin Renal Support Feline Dry; Diet B Hills Prescription Diet k/d Feline with chicken, dry) were fed to cats with CKD IRIS stage 1 and 2 for 6 months. Cats consuming diet A had significant loss of body weight and lean body mass, whereas cats fed diet B had a significant increase in body weight and no change in lean body mass. More calories were consumed by cats eating diet B than diet A. Serum creatinine increased in both groups, but a greater increase was observed in cats consuming diet A. Biomarkers of kidney function were more stable for cats eating diet B[62] but these changes were small.

The interested reader is referred elsewhere for recommendations regarding the management of hypertension[39,63-66], renal proteinuria reduction and RAAS inactivation[67-69], and management of CKD- MBD (CKD- mineral bone disease) including the use of calcitriol.[19]

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