Growing a Feline-Friendly Practice: Get Positive CATtitude
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IMPROVING A CAT’S CLINIC EXPERIENCES
In many clinics, some veterinarians and other team members do not enjoy working with cats because they may feel anxious about getting hurt. This fear can be reduced by understanding why cats feel that they need to defend themselves, learning to identify the cues, managing the interactions in a positive manner, and making relatively minor changes to what the cat is exposed to.

The basis for working cooperatively with cats is being empathic to their nature and behaviors and trying to imagine what their experience is like. Cats are a species with a social structure unlike ours. We need to look at cats differently and adjust our interactions as well as the physical facility to reduce the strangeness and threats that cats experience in the veterinary clinic.

Relying on the “fight or flight” response, cats attempt to escape situations they view as dangerous. From the perspective of a cat, humans are, (and what we do is), dangerous. As a result, we see frightened and defensive cats every day. Cats try to avoid physical confrontation through the use of intimidating sounds and posture. This small creature feels more threatened than we do, so we need to refrain from becoming frightened ourselves.

Reading and understanding the cues and signals that cats use is important to reducing their fear. It also allows us to respond respectfully. We can learn to avoid using signals that are hostile (e.g., scruffing, making shushing/hissing sounds, looking into their faces).

Examples of Practical Applications
1. If a cat is uncooperative, a comprehensive physical examination can usually be done using a towel as a protective barrier. Facing the cat away from you is less threatening for her. Confining the cat between your legs as you sit on the floor provides adequate, persistent, firm, restraint that is reassuring rather than frightening.
2. Swaddling a cat’s forelimbs and torso may help with blood and urine collection, placing the cat in lateral recumbency for cystocentesis and making the medial saphenous vein. This vein is also a superb choice for catheter placement and administration of intravenous medications. If the cat is allowed to have her front end in a sternal position while the back end is in lateral recumbency, he/she may struggle less.
3. Allow the client to be with the kitty as much as, and whenever, possible.
4. Recognize that a persistently elevated systolic value above 170 or 180 mm Hg probably represents true hypertension rather than the stress response. If in doubt, repeat the value later during the visit.
5. Feliway™ (Ceva Animal Health), a synthetic analog of a feline facial pheromone, generally has a calming effect on cats. Spray it into kennels and carriers and even on your clothing before handling an anxious cat. Let the substance evaporate for a few minutes before placing the cat into the sprayed space. Feliway diffusers plugged into treatment and hospitalization areas, as well as reception and consultation rooms, can help patients relax. (www.feliway.com)
6. Elevated blood glucose and glucosuria may be a result of persistent stress. A diagnosis of diabetes, therefore, should be confirmed by finding an elevated serum fructosamine.

In the wild, the number of feral cats living together depends on the availability of resources: food, water, privacy and safety, latrine availability, and sexual partners. This results in little competition and a social structure that does not require sharing or taking turns. Stress is minimal unless there is a lack of resources. Aggressive communication signals developed in order to keep distance between individuals.
and prevent contact with outsiders. Physical injury is to be avoided as a cat must be able to hunt and protect herself. If there are enough resources, the natural grouping consists of a colony of related female cats with their young, who they jointly defend and nurse. Males are relegated to the periphery and vie for the prime breeding spot, only one mature tom usually living with the group.

**Feline Signaling: Reading Their Cues**

**Tactile Sense**

Touch is very important to cats. They rub against each other (allorubbing), against us, and against inanimate objects. Whether full-body rub or a flank, tail, cheek or other body part, this is believed to be an affiliative behavior and is seen between members of the same social group, feline or human. Rubbing is not only tactile, but is also a means of depositing scent. Cats often rub against us; unfortunately, we often misinterpret it as a request to be fed.

Allogrooming (mutual grooming) may precede a playful attack, follow a stressful interaction, and appear to be conciliatory or may simply be grooming. Kneading and treading occurs in adults, either as a kitten-regressive behavior, or as a component of sexual interaction.

The neck bite/scruffing is a signal that is used in three contexts: transportation young kittens, sexual, and dominating another cat in a fight. Our use of scruffing fits most closely with the last and probably does not belong in a conciliatory, respectful cooperative setting. (See AAFP and ISFM feline-friendly handling guidelines.)

**Olfactory Cues**

The role of smell and scent in feline communication is something we human beings are ill-equipped to appreciate. It has been estimated that the size of the olfactory epithelium in cats can be up to 20 cm², whereas people have only 2 to 4 cm² of olfactory epithelium. While olfactory signals may be left by several methods, the one that is most problematic for people is urine spraying. This is a potent communication method that we fail to appreciate. Other forms of olfactory messaging are cheek marking an object or individual, scratching to leave scent from glands below the footpads, and midden (i.e., leaving a deposit of feces uncovered in a strategic place). All of these have several advantages over visual cues. The message exists over time and in the absence of the sender, allowing for remote communication without the potential for conflict that directs interaction risks. This is especially useful in areas with poor visibility and at night. In this way, these signals help cats spread out over space, as well as time-share territory. The disadvantage of this form of communication is that the sender cannot change the message once it has been deposited; it cannot be altered or removed and no adjustments can be made in response to the recipient’s reaction. So, urine marking in the home is an attempt to signal to the other cats when “I was ‘here’” and to establish a routine, so that the cats can keep a distance by time-sharing the same space without needing to come into conflict. Every time we remove the urine, we interfere with this communication!

Because of our less developed olfactory sense, we fail to “read” the cues a patient may be giving us and are unable to fathom the overwhelming olfactory messages from previous patients and substances used in the hospital that the clinic experience must present to cats.

**Visual Cues: Body Language (Posture, Face, Tail)**

Body language and facial expression are extremely effective at maintaining or increasing distance between hostile individuals. This requires an unobstructed view, adequate ambient light, and, unlike olfactory cues, that the two individuals are in the same space together. Body posture gives the big picture of emotional state (see Figure 1), but facial expression (eyes, ears, whiskers, mouth, visibility of teeth) provides the finer details and changes more rapidly. In a clinic setting, for us to appreciate the mental/emotional state of an individual, to avoid provoking them and getting hurt, it is extremely important to watch and interpret facial changes.
Figure 1. Interpreting a cat’s body posture

As a species that generally leads a solitary existence, survival depends on speed, stealth, self-reliance, and outsmarting others. As a consequence, cats may “bluff.” When they act aggressively, they are generally hiding fear; “stoicism” hides vulnerability; subtle changes in behavior mask significant illness. Body postures communicate confidence and physical prowess that may not be present. Keeping a threat at a distance may eliminate the need for a physical confrontation. The arched back “Halloween cat” typifies this façade of confidence. Making oneself smaller, on the other hand, to minimize threat and evade attention is portrayed by a crouch and withdrawal. In these postures, the weight remains on all four paws so that flight or chase remains possible. A cat feeling less fearful does not need to be on his or her feet. However, an extremely fearful threatened cat will roll exposing his or her abdomen with all four feet ready for self-defense. This cat will also be showing all of its weapons (nails and teeth) and be screaming.

Cats have extremely mobile ears. (See Figure 2) When the ears are forward, a cat is listening and is generally relaxed or alert but not emotionally aroused. Turned laterally, flat “airplane ears” indicate that the cat is more fearful or feels threatened. When ears are back and tight to the head, the cat is feeling very threatened and frightened. This cat will have a partially or fully open mouth and be hissing, spitting, yowling, or screaming. The cat will protect itself if we fail to reduce the perceived threat level. Ears turned back but erect indicates the most reactive and aggressive state. In this case, the mouth will be closed and the cat will be emitting a low growl with or without swallowing. This is the cat to be apprehensive of.
Vocalization
This form of communication requires that the recipient is present; it has the benefit of being easy to adjust from moment to moment. As with other signals, cats have a well-developed repertoire of sounds to convey a need or wish to increase the distance between individuals. The sounds made for encouraging socialization are a trill/chirrup, purr, puffing, prusten, chatter, miaow, and sexual calling. The cat that is open-mouth screaming is highly aroused but is probably less aggressive than the cat that is close-mouthed growl/wah-wah/mowling.
Cats use a combination of these different signals in any situation. We have to learn to look for all of them and interpret them together.

FROM A CAT’S POINT OF VIEW: REDUCING THREATS IN YOUR CLINIC
We need to reduce exposure to predators (dogs, people, other cats) and other perceived threats. Looking over our clinic/hospital environment, what can we do to reduce the stress and threat level of the physical and social environment? What things or events assault the five senses of a cat? How can we make positive changes to these? Table 1 shows a chart that can be completed by the clinic team.

Table 1. Chart for evaluating a clinic’s perceived threats to cats

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Handling (Examination, Hospitalization, Diagnostics, and Treatments)
The goal is to handle our patients respectfully and provide an appeasing environment to build positive, long-term relationships. This is achieved by reducing threat and, thus, the cat’s need to react defensively. Avoid doing things in a way that use threatening feline body language or tone. The aggressive cat is upright, stiff-legged, large; sit down to examine him.
Never stare a frightened cat in the eyes: examine cats from behind and, other than for ophthalmic evaluation, avoid direct facial viewing. Look at the cat’s face using a sideways glance with hooded eyelids. A slow blink is a reassuring signal to a cat similar to a smile.

The aggressive cat growls and uses low tones; use light, upper register tones, perhaps chirruping as cats do when they are relaxed with conspecifics. Shushing a cat to try to calm her as we might a child is the equivalent to hissing at her. Short repetitve sounds should be avoided, since these may resemble spitting rhythms. Purrs, chuffing, trills, and chirrups are welcoming sounds.

When cats feel secure and safe, even just able to hide their faces in an elbow or a towel, they allow most procedures. Try to keep all four of their paws on the floor and avoid changing their body position as much as possible. A comprehensive examination, blood and urine collection, body temperature and blood pressure evaluation can all be done without changing the cat’s position. Examine her in the base of her own carrier if the lid can be removed. Don’t hang a cat’s forelimbs over the edge of a table for jugular venipuncture. For an already frightened individual, additional lack of support under the paws is not reassuring.

Reaching into a kennel to pick up a patient blocks the light; to the cat you appear as a looming frightening stranger. Instead, approach the opening of a kennel from the side so that some light still enters. Do not block every chance for escape; if the possibility to have some control over her environment and situation exists, she will be much more cooperative. Because cats rely on flight and fight for survival and are not reliant on others, when it comes to restraint, the mantra holds true: Less is more! Cats inherently resist intimate handling and restraint. By restraining them, we take away their sense of control and cause them to react. It is very easy to condition negative emotional responses. Scruffing is strongly discouraged as it is an act of dominance that cats may resent. Cat bags, masks, and gloves all carry the scents of similarly terrified patients plus other sundry smells (anal gland secretion, pus, blood, halitosis, etc.) A towel is all that is needed to wrap a cat in, in order to protect the handler. Remember, a cat would rather flee than attack. Similarly, stretching is an inappropriate and unnecessary way to apply restraint.

Other Considerations
As cats age, they tolerate less time in the clinic. Siamese cats are especially prone to becoming depressed. Three days is about as long as a cat can stand the indignities and anxieties of hospitalization, even with daily visits from the owner. Consider capping intravenous catheters and send patients home, having them return for outpatient care. Even for in-hospital care, capping catheters off overnight avoids alarms, which can keep patients awake, and allows greater ease of movement. In either case, administer the overnight fluid volume subcutaneously.

Because cats “see” the world in overlapping clouds of smells, we should strive to provide familiar smells and reduce foreign, medicinal smells. Client-worn shirts or toys from home are helpful in cages. Because cats’ sense of hearing is tuned more finely than ours, a quiet and reassuring environment is desirable. Cats should not be exposed to the sounds of predators, namely barking dogs. Reducing noises should be addressed when using certain induction agents as some enhance hearing (e.g., ketamine).

Avoid changing a cat’s diet during hospitalization, as this is likely to result in inappetence and possibly the development of an aversion. If a change in diet is required for therapeutic reasons, try to make that change gradually at home.

Taking a thorough history is especially important given cats’ tendency to hide illness. Listening carefully to clients and their concerns is extremely important. Often clients detect changes that represent real problems. This is probably more common than the client who is blissfully unaware of significant health problems. By asking open-ended questions, we elicit a more detailed history than using only specific questions. For example, asking, “Have you noticed any changes in the contents of the litter box?” will probably evoke a yes or no answer. Asking something like, “What does his stool look
like?” initially, followed by: “Would you describe it as hard pellets, moist logs, cowpie, or colored water? When did you first notice this?” will probably provide more useful answers. “Is there anything else?” is a very valuable question.

Schedule a recheck appointment to evaluate the effect of any medical or nutritional therapy. Reassessing important variables (e.g., body weight, body condition score, previously abnormal laboratory results) and updating the patient history allows us to provide better care for our feline patients. Care of the client is essential to providing complete patient care. It is only through listening to, educating, and working with the client that we are able to offer the very best veterinary care.

**Facilitating Finances**

The Bayer study showed that clients want costs spread out over time. Fear of large bills is another significant factor preventing owners from bringing their cats to the clinic. Many practices have wellness plans. Those interested in investigating the idea can have a look at an income-generating, customizable program called Partners in Wellness (www.partners-n-wellness.com). Additionally, directing clients toward pet health insurance for both preventive and accident/illness coverage before their cats need it is sound medical advice. This could save lives otherwise lost because the owner hesitated to seek care or decided to euthanize the pet because of financial concerns.

**References**

6. Hide Perch Go and Cat Sense: www.spca.bc.ca/welfare/professional-resources/catsense/
Improving Compliance of Feline Clients
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While the number of cats kept as companions in North American homes is increasing, the number of feline visits to clinics has been declining since 2001. Based on the AVMA’s 2007 pet ownership and demographics survey, there are 13% more cats than dogs, yet cats fail to receive the same degree of veterinary attention. In small-animal practices, dogs represented 59% of office visits, cats only 39%. The 2011 Bayer Brakke study further noted three client-driven factors that limited the number of feline visits:

1. Inadequate understanding of the need for regular preventive health visits other than for vaccination.
2. Resistance to bringing a cat to the clinic because of the distress caused by placing a cat into a carrier and making the trip to the clinic.
3. The cost of veterinary care, in particular the frequency and size of price increases. (The economy is a separate, external factor.)

In November 2012, an online survey was conducted by Bayer of 401 veterinary practice owners across the USA. The Bayer Veterinary Care Usage Study III: Feline Findings noted that 78% of veterinarians believed that better care for cats represented one of the most significant, missed opportunities for the profession. Yet, while 70% of veterinarians were familiar with the earlier Bayer-Brakke studies, and while most veterinarians recognize that cat owners consider a clinic visit to be stressful for themselves and their cats, nearly one-third of practices do not have staff trained on how to make visits less stressful for clients. Additionally, relatively few practices have adopted procedures, such as: exam rooms used only for cats (35%); cat-only waiting areas that are physically and visually separated from dogs (18%); and cat-only days and appointment hours (11%). The study found that 46% of veterinary clinics surveyed had recently started taking specific steps to increase visits among current feline patients, attract more cat-owning clients, and make their practices more “cat friendly”.

Part of the lack of awareness (at best) or reluctance (at worst) for making simple, inexpensive changes in attitude and facility is that many veterinarians and veterinary staff members prefer, or feel more comfortable, working with dogs than cats. Veterinarians also indicated that dogs are easier to diagnose.

The goal of this set of three presentations is to look at practical steps to overcome these obstacles to routine veterinary care for cats in order to benefit cats and their human companions with resulting benefit of clinic growth.

IMPROVING CLIENT COMPLIANCE
The verb “to comply” means to act in accordance with a wish or command (Oxford), to conform, submit, or adapt (as to a regulation or to another’s wishes) as required or requested (Merriam-Webster). For clients to comply with our recommendations, they have to understand fully and be able to perform actions that we are asking of them. We need to engage them in the importance of these actions. Thus, understanding (education) and on-going caring communication are needed to enhance client compliance.

Many clients believe that cats are self-sufficient, have very few needs, and are low-maintenance pets. They don’t understand that cats live as solitary hunters because they eat small prey; this means that they lack the supportive resources of a society. To avoid showing weakness, they hide signs of illness very well. The first opportunity we have to improve compliance is to teach people to recognize
the subtle signs of sickness. Everyone on the veterinary team also has to recognize that any admission of illness by a cat may signal a problem that has been going on for a longer time than one believes. The following clinical signs are things that clients can be taught to look for through newsletters, the clinic website, Facebook and other social media, as well as direct client emails.

**Subtle Signs of Sickness**
www.healthycatsforlife.com

Clients need to know what to look for and how significant minor changes such as the following can be:

1. **Inappropriate elimination:** Regardless of how “deliberate” it may seem to be, when a cat is avoiding or not using the litter box, they are trying to tell you something. This message may be of physical discomfort or psychological distress. Physical causes include inflammation of the bladder or bowel, arthritis, hyperthyroidism, diabetes, dementia. Psychological distress may be from social disturbance, boredom, the lack of opportunity to act the repertoire of cat behaviours, anxiety due to other animals, children or adults.

2. **Changes in interaction:** Changes in how a cat interacts with people, other animals or his/her environment may indicate pain or distress.

3. **Changes in activity:** A decrease in energy may be abrupt or gradual. The latter is often attributed to “just getting older”; however, as there is no medical reason that a healthy individual should “slow down” due to increasing age, a cause should be sought. Dehydration, pain from anything, including arthritis, hypokalemia are some of the problems that should be evaluated. The reverse is also true: an increase in energy in a previously normal cat may be an indicator of incipient illness, most notably, hyperthyroidism or hypertension.

4. **Changes in sleeping habits:** This refers both to pattern of sleeping (times of the day and night), as well as postures. A cat with pain or with dementia may either sleep for longer or for shorter periods than previously. With FIV infection, the latter may occur. Night-time yowling suggests a decline in vision or hearing, hypertension, hyperthyroidism, pain or dementia.

5. **Changes in food and water consumption:** As with sleep, this refers not just to quantity, but also to changes in behaviours associated with these activities (where, how often, amount at each instance, body posture, etc.).

6. **Unexplained weight loss or gain:** As gratifying as it is to see rapid weight loss in a previously obese patient, even for those on appropriate dietary regimes, it isn’t often a dramatic change. Oral pain may result in inappetence. Gradual weight loss may be related to ageing but should be monitored and investigated. Weight gain is most often from excess calories but could also be due to abdominal or thoracic fluid accumulation. Helpful tools include repeated body weight, body condition score and percentage weight change assessments.

7. **Changes in grooming:** Excessive grooming may be due to a skin irritation (allergy, fleas, dryness), a neuropathy, or psychogenic (as a way to release endorphins and reduce stress). A decrease in grooming is often associated with pain, often arthritic or oro-dental. Hairballs may be a sign of dermatologic, psychogenic, altered digestive motility or pain.

8. **Signs of stress:** Along with aforementioned inappropriate elimination and overgrooming, signs of distress include hiding, chewing on non-food items, a flicking tail, ear placement further back than normal.

9. **Changes in vocalization:** Night-time yowling is but one example. Others include a change in tone, pitch, urgency and frequency of vocalizing.

10. **Bad breath:** Numerous oral and dental conditions result in halitosis: periodontal disease is extremely common in cats but infected ulcers, tumours, sialoadenitis, abscesses and spread through grooming of odour from anal sacs or an infected body region.
Yet, even recognizing that their cat has a problem may not be enough to get the client to bring them in to the veterinarian. Screening to proactively identify disease early and to provide solid medicine can be an even harder sell because people do not like bringing their cats in to the clinic. Many cat owners would rather provide care at home or even skip any form of consultation unless there is something serious going on! This offers us the second significant opportunity to improve the lives of our patients and be of help to our clients.

**GETTING CATS TO YOUR CLINIC**

It is no fun taking a cat to a veterinary clinic (for the owner or the cat)! All veterinary team members should be trained in teaching clients how to make the trip less stressful, starting at home, while in transit, and once they arrive at the clinic. This conversation begins when the client calls to make an appointment or at the first visit with their cat. The American Association of Feline Practitioners (AAFP) has a free downloadable client handout entitled: *Getting Your Cat to the Veterinarian* (http://catvets.com/uploads/PDF/2011FelineFriendlyClientHandout.pdf). Clicker training can be used to help create positive associations. Catalyst Council (www.catalystcouncil.org) has created excellent videos that clinic teams and clients can watch to facilitate learning.

The frightening experience begins at home. Imagine the scenario from the cat’s point of view: The carrier comes out, your caregiver is nervous, she chases you around and tries to force you into the carrier. You resist and may resort to self-defense. There are smells of human sweat, fear, maybe even blood. You may feel so anxious that you soil yourself! Eventually you are in the carrier. Everyone is exhausted. Then you are moved into a “car” that moves without you moving. You may be a bit nauseated; certainly you are scared. You cry out repeatedly. You may vomit or soil yourself. Then the “car” stops and you get carried on a noisy and unfamiliar street and into a place with overwhelming smells and sounds! Help! And you are already aroused and anxious….look out!

We can reduce the stressors the cat encounters, or, in the case of a new cat, prevent the stressors from occurring by teaching or habituating the cat to associate positive experiences with the carrier, the car, and even the clinic. By leaving the carrier out (or using a Hide Perch Go box/carrier) so that the cat sees it routinely and enters it for treats or other rewards, we dampen the initial tension and fight. Taking the cat on short car rides that are unassociated with the clinic helps recondition the cat’s negative associations with the clinic. Finally, taking the kitty to the clinic to be fussed over or only to get a treat will help teach the cat that the clinic isn’t necessarily a horrible place.

**TAKING THE HOUSEHOLD CAT INVENTORY**

While there are a lot of cats who never get taken to the vet, there are a lot of cats living with existing clients we never see. We don’t even know that they exist! If the cat is well or if the client has had a really bad experience in the past with a cat (or anticipates “bad behavior” from a cat), they are unlikely to voluntarily bring them in for preventive care. We need to ask whether they have any cats or any other pets when they bring their dog or cat in for whatever reason, this will help to identify the unserved patients.

**IMPROVING THE CLINIC EXPERIENCE**

From the client’s point of view: *It wasn’t fun to bring her, she isn’t happy about being in the clinic and it isn’t fun watching her be “manhandled.”* Once at the clinic, with fear and stress already in place, minimizing or eliminating any further perceptions of threats is extremely important. This requires trying to see the clinic from the point of view of a cat. The second and third of these presentations will speak specifically to these matters.

Making the environment more “feline friendly” can be as simple as having visual barriers in the seating/waiting area to prevent cats from seeing dogs. Covering the carriers with a towel will also help
so that cats don’t see each other. If possible, have separate, cat-only waiting area. Reserve at least one examination room only for cats to reduce the smells of predators and to be able to furnish it with cat exam and comfort in mind.

Train all staff in respectful cat handling. An excellent and comprehensive resource is the AAFP and International Society of Feline Medicine (ISFM)’s Feline Friendly Handling Guidelines, downloadable at: www.isfm.net/wellcat/UK/FFHG.pdf. It is well worth reviewing and refining cat examination techniques with the goal of making them less threatening. Because value is “perceived worth” and because every visit is a valuable opportunity to educate the client, communicate with the client and the cat throughout the entire procedure. Source and provide feline-friendly medications, being sure to follow up one or more times with the client to find out how the patient is doing and if the client needs a refresher course on how to administer the medications. Be sure to send home an exam report with home care instructions for the client to refer to. Schedule rechecks appointments or the next wellness visit before the client leaves the practice.

The AAFP has created the Cat Friendly Practice program through which any interested clinic can raise its cat care IQ. (catfriendlypractice.catvets.com)

Having a library of YouTube links or making your own clinic “how-to” videos is extremely helpful. YouTube videos made by lay people may have the advantage of being more convincing rather than those by healthcare professionals. Find ones that your staff and you, as well as a client, think are best. There are many good links. Examples of useful illustrative clips to have on hand include how to:
- Give your cat a pill (see below)
- Give subcutaneous fluids: www.youtube.com/watch?v=OLOVw3S5w4Ns
- Administer insulin: www.youtube.com/watch?v=XeZgKLflJn4
- Measure blood glucose: www.veterinarypartner.com/Content.plx?A=605
- Use an inhaler for asthma medications: www.youtube.com/watch?v=INF1W8uaPEA
- Feeding with a feeding tube: contact me at hypurr@aol.com
- Change a KittyKollar (video) and Living with an E-tube (handout): www.kittykollar.com

Syringe feeding, brushing teeth, etc. are also available. Cat caregivers like to show their skills and help others.

Similarly, having a selection of web resources that you have vetted and feel comfortable with, guides clients to reading materials when they want to learn more about their companion’s medical condition.

Cornell University has a series of videos on a number of procedures and diseases at www.partnersah.vet.cornell.edu. They include: Brushing your cat’s teeth, Giving your cat a pill or capsule, Giving your cat liquid medications, Taking your cat’s temperature, Trimming your cat’s claws. Other free videos include: Caring for your diabetic cat, Gastrointestinal diseases in cats, Cat owner’s guide to kidney diseases, Managing destructive scratching behavior in cats and Pet owner’s guide to cancer.

Everything on the Feline Advisory Bureau has been created by the ISFM and is excellent: fabcats.org/owners. They have an extensive library of handouts on medical conditions, as well as general cat care, including several videos.

Feline Chronic Kidney Disease: www.felinecrf.org
SUMMARY

By not seeing cats because we don’t know they live with clients or because clients are unwilling to bring them in, we lose the opportunity to:

- Provide wellness care
- Detect disease early when we can prevent or alleviate suffering and save expense
- Protect life and enhance welfare
- Build trust with our clients
- Increase clinic visits
Understanding Client Satisfaction and How to Measure it
Rob Wilson Rogers, BA, BCom, MBA

SESSION 1: WHAT CLIENTS REALLY EXPECT
Find out how you listen to the voice of your customer. It’s critical.

It’s a fact that the quality of a customer experience is directly linked to profitability. Why? Because satisfied customers come back more often and refer you to their friends.

The reality is that visits to veterinary clinics are down across North America. No doubt the recession is partly to blame, but this trend started long before 2008.

So what’s really going on? The state of the economy doesn’t tell the whole story because owners are still spending lots of money on their pets. And internet pharmacies and premium food sales have never been stronger.

Perhaps other factors are at play. Have you thought long and hard about customer service and whether or not your value proposition makes sense? Do customers really understand the value of the services you provide?

Despite significant scientific advances, many of us still struggle to understand what pet owners really expect and how to create an experience that exceeds expectations so they keep coming back and recommending us to friends.

The real challenge is putting ourselves in their shoes. The gap between the quality of service we think we deliver and what the customers think they receive and how we value a job well-done is different.

The first session examines this perceptual divide between the practitioner, the clinic and the pet owner and how you see your customer experience through their eyes.

SESSION 2: HOW YOU MEASURE YOUR CLIENT EXPERIENCE
Learn how you collect actionable feedback - see data from successful clinics.

Customers who are surveyed about their satisfaction are inclined to do more business, are half as likely to defect and more profitable than customers who aren’t surveyed.

Every textbook written on the subject of customer service will tell you that the first step to satisfying customers is asking them what they think of the service they receive. Why do we overlook this important step? Are we afraid of what they’ll say or confused about where to start?

The fact is, every customer has an opinion and most are willing to share it. So get over the fear of asking. Research shows that asking for feedback demonstrates openness and transparency and builds trust that can lead to loyalty. And as a bonus, you’re sure to get great ideas and new ways to save time and money.

But where do you start? Just do what other successful organizations do. Find the best survey, ask one or two customers every day and make improvements where and when customers think you underperform. It’s that easy.

In this second session we’ll look at an affordable web-based analytics tool and data from successful Canadian practices. You’ll see what satisfies customers and the difference between a great customer experience and all the rest.

We’ll also examine the importance of emphasizing wellness and prevention early and how it leads to regular checkups and increased loyalty.

SESSION 3: HOW YOU MAKE EVERY EXPERIENCE COUNT
Get service ideas that help build positive word of mouth.
30% of veterinary clients come on referral. In 2012, 54% of Canadians who had a positive service experience told 13 other people - up from 9 in 2011.

No matter how successful you are in keeping customers - attracting new ones is job one. The short lifespan of companion animals, an aging pet population and natural customer attrition necessitate the need to add/replace 15–20% of a practice’s customer base every year.

What’s your growth strategy? Advertising is expensive. The best way to grow is through referrals. And more than two decades of loyalty research confirms that customers who come on referral spend and visit more, take less time and energy to service - and are more profitable.

So what’s the trick? It all starts with an exceptional customer experience. Sure we know that being attentive and sensitive and the soft human side of the practice is important - but what about the way we look or how we personalize every customer interaction?

Whether we like it or not, customers judge us on what they see and don’t really understand what we do. First impressions count. If your operation doesn’t look professional or there are surprises when the bill is presented, it’s highly unlikely that they’ll be enthusiastic to recommend you.

This third and final session examines the importance of appearance, precision and full disclosure and provides proven low and no-cost ideas to help you satisfy every customer and build your business.
The following papers are compiled to accompany the presentations scheduled in the continuing education sessions at the convention. The proceedings are organized by day and by stream as follows:

**THURSDAY, JULY 11**

Companion Animal – Dentistry  
Companion Animal – Feline Nutrition  
Companion Animal – Canine Theriogenology and Pediatrics  
Companion Animal – Ophthalmology  
Equine – Take Home Stud Practice  
Equine – Conditions and Management of the Periparturient Mare  
Bovine – Reproduction  
Bovine – Respiratory Disease  
Animal Welfare - Ethics and Issues  
Animal Welfare – Pain Assessment in Cats
Practical Periodontal Disease Pathophysiology and Diagnosis: Part I
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INTRODUCTION
Periodontal disease is the most prevalent disease of dogs and cats over 3 years of age. Periodontal disease is caused by a bacterial biofilm (plaque) and the associated inflammatory response. It may be potentiated by, but not limited to, malocclusions, crowding and rotation of teeth, systemic disease, nutritional status, individual patient susceptibility, genetics, trauma, and increased tooth to jaw size ratios. It is a multifactorial, complex, hidden, ubiquitous disease. Periodontal disease destroys the periodontium (periodontal ligament, alveolar bone, cementum, and gingiva). Periodontal disease is the loss of the periodontal attachment apparatus. Since 75% of these structures are identified below the soft tissues (gingiva and alveolar mucosa), a thorough clinical subgingival evaluation and intraoral radiographs are necessary to diagnose and assess periodontal disease. Therefore, general anesthesia is necessary to diagnose and treat periodontal disease. It is a disease below the gumline (subgingival)!

It is accepted that oral infection/inflammation is associated with many systemic conditions in human medicine. There are few good studies in the veterinary and human literature associating oral infection and inflammation with systemic disease. Nevertheless, scientific data has emerged to associate oral infection with systemic disease. (Note: The word “associate” was specifically chosen, as there is no evidence, at this time, suggesting a cause-effect relationship.) Acute-phase inflammatory proteins have been demonstrated with oral infection in both humans and dogs. Periodontal organisms have been identified in renal, hepatic, and cardiac tissues of the dog, and the association with the infection/inflammation systemically is suggested.

The normal gingival sulcus depth in a dog is 0–3 mm and 0–0.5 (1.0) mm in a cat. Periodontal disease is the loss of the periodontium (attachment loss) and may or may not be associated with periodontal pockets. Periodontal pockets are a crucial factor in fostering anaerobic environments (pseudopockets, infrabony [intrabony] pockets, and suprabony pockets) and must be treated to help control pathogenic bacterial biofilms.

The development of periodontitis starts with the pellicle (a biological conglomerate of organic molecules, glycoproteins, epithelial cells, etc.) that adheres to the surface of the tooth. The pellicle serves as a substrate for the attachment of bacteria to form plaque (a synergistic biofilm of bacterial colonies). Plaque is the cause of periodontitis. The formation of plaque involves bacterial adhesion followed by colonization and maturation. Periodontitis is caused by the combination of the bacteria and their toxins, and the host inflammatory and immune response. Early bacterial colonization includes Gram-positive aerobic cocci, but the synergistic bacterial populations quickly switch to Gram-negative anaerobes and spirochetes deeper in the periodontal pockets. Bacterial products such as ammonia, volatile sulfur compounds, and proteolytic enzymes contribute to the destruction of the periodontium. The host inflammatory response, including cytokines (interleukin-1β, interleukin-6, tumor necrosis factor-α) released from macrophages secondary to bacterial cell wall lipopolysaccharide stimulation, matrix metalloproteinases (MMP-8, MMP-1) that degrade collagen of the periodontal ligament, elastase (break down collagen and elastin), and prostaglandins (PGE₂) are directly responsible for tissue damage and/or stimulate osteoclastic bone resorption (PGE₂, IL-1β, TNF-α). The calcium carbonate in the saliva of cats and dogs combines with the plaque to form calculus. Calculus increases surface area for bacterial attachment and can mechanically disrupt and damage the gingiva.

Treatment plans can be designed based on the individual tooth stage as well as the overall periodontal stage of the oral cavity. Treatment of periodontal disease involves the combination of a professional periodontal cleaning, intraoral radiographs, periodontal surgery, client education, and home care. Anesthesia, professional examination, periodontal probing, charting, and intraoral
radiographs are all required to successfully diagnose and treat periodontal disease. Treating and controlling other systemic diseases such as cardiac disease, renal disease, diabetes mellitus, pancreatitis, uveitis, immune system deficiency, and other conditions often require controlling and treating periodontal disease.

American Animal Hospital Association Dental Guidelines and Canine and Feline Life Stages Guidelines recommend annual evaluations of the oral cavity. The recommended time to start professional evaluations and cleanings, in order to prevent disease, is in the 1st–2nd year of life.

**Clinical Signs of Periodontal Disease**

The clinical signs of periodontal disease are often hidden and insidious. Halitosis, gingivitis, supragingival plaque and calculus, reluctance to chew, head shyness, pawing at the mouth, dropping food, sneezing, and nasal discharge are clinical signs. Unfortunately, many of those clinical signs require astute client observation and/or careful questioning from the clinician. Most commonly, there may be no obvious signs.

**Conscious Oral Examination**

Periodontal assessment begins in the examination room with the client and the conscious patient. A complete medical and oral history, general physical exam, and conscious oral examination are necessary. A complete history and evaluation of the chief complaint are investigated. Questions such as, but not limited to, onset, duration, environment, chew toys, oral health care, current medications, diet, past illness, past anesthetic episodes, behavioral changes, etc., are explored. Many patients with oral disease do not have obvious clinical signs.

The maxillofacial skeletal is palpated and the eyes retropulsed. The three basic skull types are brachycephalic (e.g., Pugs, Bulldogs, Persian Cats), mesocephalic (e.g., Labrador, DSH), and dolichocephalic (e.g., sight hounds, Collies). The regional lymph nodes and salivary glands are palpated. Facial symmetry and occlusion are noted. The range of motion of the temporomandibular joints should be palpated and the patient observed for pain and/or difficulty in opening and closing the mouth. The lips and mucocutaneous junctions should be observed for ulcerations that might indicate an autoimmune disease. Finally, the dentition is evaluated and the teeth counted to determine if all teeth are present. Discolored teeth, persistent deciduous teeth, root and furcation exposure, oral mucosal lesions, sinus tracts, tongue lesions, oral masses, plaque, and calculus are noted.

The owner is counseled that, although we do our best to estimate the extent of disease, anesthesia, anesthetized oral exam, periodontal probing, and intraoral radiographs will often identify hidden disease subgingivally, and the conscious exam and plan is our best good faith estimate.

**Anesthetized Examination**

It is impossible to completely examine the oral cavity in a conscious patient. At best, we can estimate the extent of periodontal disease, identify fractured teeth, and see obvious soft-tissue disease. Anesthesia is required (www.avdc.org AVDC position statement) to accurately assess periodontal disease, fractured teeth, and other oral pathology.

While the patient is under anesthesia, a full oral examination and dental charting are performed. Periodontal indices can be found at the AVDC website (nomenclature www.avdc.org).

During the periodontal examination, crowded teeth, missing teeth, rotated teeth, mobile teeth, teeth with furcation exposures, gingival recession (root exposure), sinus tracts, gingival enlargements, and periodontal probing depths are noted. (The normal gingival sulcus depth in a dog is 0–3 mm and less than 0.5 to 1.0 mm in a cat.)
A gingival index of 1 includes inflammation and swelling of the gingiva with no bleeding during periodontal probing. A gingival index of 2 includes bleeding during periodontal probing. A gingival index of 3 includes spontaneously bleeding of the inflamed gingiva prior to periodontal probing.

Furcation exposure (involvement) occurs when a periodontal probe can extend between the roots, under the crown, of multirooted teeth as a result of attachment loss. A stage 1 furcation involvement exists when the probe extends less than halfway. A stage 2 furcation involvement exists when the probe extends greater than halfway. A stage 3 furcation exists when the probe extends from one side to the other, through and through.

Gingival recession and root exposure can occur with or without associated increased periodontal probing depths. Regardless, if the root is exposed due to gingival recession, there is periodontal disease because periodontal attachment is lost.

**PERIODONTAL DISEASE STAGES**
Veterinary dental nomenclature allows us to classify periodontal disease into stages (www.avdc.org). A clinically normal oral cavity with no gingival inflammation and periodontitis is stage 0 (PD0). Gingivitis without attachment loss (normal height and architecture of alveolar margin) is stage 1 (PD1). Stage 2 (PD2) is early periodontitis with less than 25% attachment loss (intraoral radiographs) and/or a stage 1 furcation in multi-rooted teeth. Stage 3 (PD3) is 25–50% attachment loss and/or stage 2 furcation in multi-rooted teeth. Greater than 50% bone loss and/or stage 3 furcation in multi-rooted teeth is stage 4 (PD4). Treatment plans can be designed based on the individual tooth stage as well as the overall periodontal stage of the oral cavity. Keep in mind that there are 42 teeth in the adult dog and 30 in the adult cat. That means 42 or 30 individual patients to diagnose and treat.

**INTRAORAL RADIOGRAPHS REQUIRED TO DIAGNOSE AND STAGE PERIODONTAL DISEASE**
In order to accurately assess periodontal attachment loss, intraoral radiographs are required. Periodontal disease is a subgingival disease, and the only diagnostic modality to fully assess the attachment of the periodontium is with imaging. The value of intraoral radiographs is well documented and undisputed as a diagnostic, treatment planning, and posttreatment tool for all disciplines within veterinary dentistry. Roentgen signs of periodontal disease include loss of the marginal alveolar bone crest, loss of the lamina dura, widening of the lamina lucida, and horizontal and vertical bone loss due to the resorption of bone. Horizontal bone loss occurs when the cortical supporting bone around the tooth and adjacent teeth is lost at a similar rate.

**PERIODONTAL POCKETS**
There are often combinations of periodontal pocket types, secondary to periodontal bone loss and gingival enlargements since types of bone loss are not mutually exclusive. However, there is often a predominant type of pocket that can be classified in order to direct treatment plans.

**Types of Periodontal Pockets**
- **Pseudopockets** are created when the gingiva enlarges (often gingival hyperplasia) and the marginal bone remains at the appropriate level. Common veterinary medications such as cyclosporine and amlodipine may cause gingival enlargement. Breed predilections exist for fibrous gingival enlargement resulting in pseudopockets (e.g., Boxers).
- **Suprabony pockets** occur when marginal bone loss exceeds gingival recession (the marginal bone is lost horizontally below the tissue).
- **Intra**(Infra)bony pockets occur when bone is lost vertically around a tooth. Infrabony pockets can be classified as one-wall, two-wall, three-wall, and four-walled (cup or crater) defects.
Common locations for intrabony pockets in dog patients include the distal aspect of the mandibular 1st molars, the furcation of the mesial roots of the maxillary 4th premolars, the mesial aspects of the mandibular canine teeth - particularly after the 3rd incisors are lost or are extracted without proper technique - and the palatal aspect of the maxillary canine teeth.

Often there are combinations of the different types of pockets. Pockets are a haven for Gram-negative anaerobic bacteria and spirochetes in the subgingival plaque biofilm and planktonic bacteria in the pocket fluid.

Click here to view the presentation, Practical Periodontal Disease Treatment Options and Home Care: Part II.

REFERENCES
References are available upon request.
Practical Periodontal Disease Treatment Options and Home Care: Part II
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Sponsored by: Royal Canin Medi-Cal

INTRODUCTION
Click here to view the presentation, Practical Periodontal Disease Pathophysiology and Diagnosis: Part I.

In order to completely and thoroughly examine and treat the oral cavity, general anesthesia is required. Periodontal disease is a subgingival disease resulting in loss of attachment of the periodontium. Assessment requires periodontal probing, visual oral examination, and intraoral radiographs. It is impossible to safely obtain accurate periodontal probing measurements and obtain diagnostic intraoral radiographs without anesthesia. Likewise, safe and complete subgingival scaling is not possible in a conscious patient. A professional periodontal cleaning requires appropriately scheduled surgical time, supragingival and subgingival scaling, polishing, dental charting and documentation, intraoral radiographs, assessments and treatment plans, client education, and home care recommendations. Treatment plans can be designed based on the individual tooth stage as well as the overall periodontal stage of the oral cavity.

A dental “prophylaxis” is a preventive medical procedure. In veterinary dentistry, the majority of our patients have existing periodontal disease, and we are rarely executing dental prophylactic procedures, by definition. A professional dental cleaning, periodontal cleaning, etc., is a more appropriate description of the services many veterinarians provide.

Periodontal disease treatment and management are required over the lifetime of the patient. Gingivitis, the first stage of periodontal disease, is reversible, whereas further stages of periodontal disease (loss of attachment) are not. Periodontal treatment includes, but may not be limited to, reversing gingivitis, arresting further attachment loss of the periodontium, treating compromised teeth (e.g., periodontal surgery, guided tissue regeneration, and extraction as indicated), and establishing a long-term recheck and home care programs.

PERIODONTAL POCKETS (DISCUSSED IN PART I)

PERIODONTAL TREATMENT AND SURGERY
Periodontal treatment begins with the complete professional dental cleaning. Periodontal surgery occurs with, and after, the oral cavity has had a thorough assessment, intraoral radiographs, and professional periodontal cleaning. Often it is best to stage the procedures so that the periodontal surgery is performed several weeks after a periodontal cleaning. If performing periodontal flaps or
guided tissue regeneration, a clean oral cavity and client commitment to home care are necessary. Soft-tissue resection and some osseous subtractive surgeries may be performed during the periodontal cleaning.

Teeth with stage 3 and 4 periodontal disease and/or periodontal pockets often require periodontal surgery to return periodontal anatomy to a manageable level for long-term professional periodontal and home care, if exodontia is not utilized to treat the significant attachment loss and infection. Periodontal pockets greater than 5 mm, periodontal probing depths beyond the mucogingival junction (whether 5 mm or not), stage 2 and 3 furcation exposures, intrabony pockets, gingival clefts, mobile incisors, loss of gingiva, and periodontal trauma require periodontal surgery.

The Periodontal Cleaning Armamentarium
Equipment necessary for a complete, professional periodontal cleaning includes, but is not limited to, ultrasonic scalers (piezoelectric and magnetostrictive [ferromagnetic stacks and ferrite rods]), hand scalers, universal curettes, Gracey curettes (only one working surface offset 70°), slow-speed handpiece for polishing, irrigation, dental probes and explorers, and dental charts.

Steps in a Periodontal Cleaning
Client consent is required prior to the initiation of treatment (be prepared to find more disease than you would expect, and prepare the client). Masks, caps, gloves and protective eyewear are worn. General anesthesia is required. The oral cavity is rinsed with a 0.12% chlorhexidine gluconate oral rinse to decrease aerosolization of bacteria. Supragingival scaling involves removing the calculus and plaque from above the gumline (hand scalers and water-cooled ultrasonic scalers - no more than 5–7 seconds per tooth to prevent thermal and concussive injury). Subgingival scaling (root planing and subgingival curettage) is where the battle of periodontal disease is won or lost. Hand curettes and some water-cooled ultrasonic scalers, with approved periodontal or universal tips, are used to clean subgingivally. Polishing involves using a pumice (fine) to smooth out roughness created in the enamel during the periodontal cleaning (no more than 3 seconds on each tooth to prevent thermal injury). The polishing cup should flare 1 to 2 mm subgingivally to polish the subgingival tooth surface cleaned during the subgingival scaling. The air-water syringe is used to irrigate the sulcus and remove debris, plaque, and polishing paste. A comprehensive oral exam and periodontal probing on at least 6 surfaces of each tooth are performed. Intraoral radiographs are obtained. The client is educated, and a home care program is recommended. A recall for the next periodontal cleaning and oral exam is set for 6–12 months.

The periodontal cleaning is not complete until client education is presented. If the procedure was a periodontal cleaning without surgery, then the client should be educated on home care at discharge. If surgery was performed, education may be delayed until the recheck appointment to verify the surgical sites are healed (10–14 days) prior to instituting a plaque-control home care program. A recall for the next periodontal cleaning and oral exam is set for 6–12 months, depending on the stage of periodontal disease, client commitment to home care, and signalment of the patient.

Periodontal Surgery
Periodontal surgery occurs with, and after, the oral cavity has had a thorough assessment, intraoral radiographs, and professional periodontal cleaning. Often it is best to stage the procedures so that the periodontal surgery is performed several weeks after a periodontal cleaning if periodontal flaps or guided tissue regeneration are being utilized. Soft-tissue resection and some osseous subtractive surgeries may be performed during the periodontal cleaning.

Clients who wish to save teeth in their pets are often owners who learned about periodontal disease prevention too late. These clients failed to receive education regarding the importance of annual and semiannual dental cleanings and home care during wellness examinations. The pets are often young to middle-aged pets where periodontal defects were detected at the pet’s first dental cleaning.
Goals of periodontal therapy include control of the plaque biofilm, prevention of further attachment loss, control and treatment of periodontal pockets (pseudopockets, suprabony pockets, and intrabony pockets), and preparing the tooth surface for reattachment of healthy periodontal tissues. Following periodontal surgery/therapy, four (4) tissues compete for the root surface: gingival epithelium, gingival connective tissue, periodontal ligament, and alveolar bone. The preferred attachments are the periodontal ligament and alveolar bone for long-term periodontal support.

Advanced periodontal surgery should not be performed if the client is not compliant with home care, the pet is not compliant with home care, or the pet is not medically stable for future anesthetic episodes to recheck and augment periodontal treatments. If there is any doubt, then extraction of an offending tooth or teeth should be executed to alleviate pain and inflammation in the patient. Prior to some advanced periodontal surgeries, having the client demonstrate and commit to home care is recommended. Finally, the application of treatment plans utilizing advanced periodontal surgery techniques cannot be learned in one lecture or laboratory. Appropriate training is necessary in order to achieve predictable results. A treatment plan including consultation with a boarded veterinary dentist (Diplomate of the American Veterinary Dental College) is often prudent. Anesthesia and intraoral radiographs are required for periodontal surgery.

**Types of periodontal surgery include, but are not limited to:**

1. Gingivectomy/gingivoplasty
2. Periodontal splinting
3. Open periodontal flaps with root planing
4. Osseous resective surgery
5. Osseous additive surgery (guided tissue regeneration)
6. Periodontal pedicle flaps and gingival grafts

**Osseous Surgery for Intrabony Pockets**

**Osseous Subtractive Surgery**

Intrabony pockets can be reduced by osteoplasty. Alveolar osteitis on the buccal aspects of feline canine teeth resulting in intrabony pockets, mesial lingual intrabony pockets of the mandibular canine teeth in the dog, and the mesial and distal aspects of the mandibular 1st molar, after extraction of the mandibular 4th premolar and 1st molar, respectively, are common locations where osseous subtractive surgery may be utilized. Intraoral radiographs and open periodontal flap surgery are required.

**Osseous Additive Surgery (Guided Tissue Regeneration)**

Guided tissue regeneration is the new formation of periodontal tissues (cementum, periodontal ligament, and alveolar bone) that had been destroyed from periodontitis. Regeneration, reconstitution of lost tissue, is differentiated from periodontal repair, healing of the periodontal wound/defect by tissue that does not fully restore the normal histological architecture. Three-walled defects, > 4 mm, have the best prognosis with GTR.

A combination of periodontal probing, intraoral radiographs, and open periodontal flap surgery is necessary to assess periodontal pockets. The palatal intrabony pockets of the maxillary canine tooth and mesial roots of the maxillary 4th premolar are often not visible on the 2-dimensional intraoral radiograph. Additionally, the location of the palatal pockets precludes osseous resective surgery due to the location of the hard palate.
Patient Selection for Advanced Periodontal Surgery (e.g., GTR, Sliding Periodontal Flaps, Periodontal Splinting)
1. A recent dental cleaning was performed, and active periodontal disease is controlled (e.g., periodontal treatments, extraction of diseased and hopeless teeth) - Generalized active periodontal infection must be treated, controlled, and resolved prior to procedures.
2. The patient is stable for additional anesthetic procedures to perform and recheck the periodontal surgery - no major uncontrolled underlying systemic, metabolic, cardiovascular, or endocrine disease.
3. The patient will accept daily home care (brushing) - often the client will need to demonstrate commitment following the initial dental cleaning and prior to the scheduled periodontal surgery.
4. The client is willing to brush the teeth daily.
5. The client is willing to follow home care instructions postsurgery.
6. The client is willing to commit both financially and emotionally to the periodontal procedure.
7. A motivated client is necessary.

Guided Tissue Regeneration (GTR)
Guided tissue regeneration (GTR) can be utilized to increase periodontal attachment of strategic teeth. Before GTR should even be considered, periodontal disease pathophysiology, the periodontal cleaning including subgingival scaling, subgingival curettage, and root planing, in addition to open periodontal flaps, must be understood.

GTR involves open periodontal flaps, +/- root surface preparations (tetracycline, citric acid, EDTA), +/- grafting materials, +/- biological modifiers (e.g., growth factors, cytokines), and periodontal membranes. Intraoral radiographs in conjunction with general anesthesia are required for assessment, treatment planning, and treatment execution.

Intrabony Periodontal Pocket Healing
During healing of periodontal pockets following periodontal treatments, gingival connective tissue, gingival epithelium, periodontal ligament, and alveolar bone compete to create reattachment to the tooth surface. The gingival connective tissue and epithelium colonize the root surface at the fastest rate and exclude the other more desirable periodontal tissues (periodontal ligament and bone) from the root surface. If soft tissue reattaches to the tooth surface, it is often in the form of long junctional epithelium, which is susceptible to breakdown and recurrence of attachment loss.

If the above criteria are met, GTR can be done with some predictability. However, if the above criteria are not met, expected outcomes may not occur, and the periodontal defect will persist.

GTR Grafting Materials
Bone grafting materials should be safe, biocompatible, nonallergenic, nontoxic, free of disease, accessible, and affordable. Grafting materials include 1) autografts, 2) allografts, 3) xenografts, and 4) alloplasts. Allografts include freeze-dried bone graft, decalcified freeze-dried bone graft (DFDBA), and mineralized bone (same species). DFDBA is considered to be osteoconductive as well as osteoinductive. Alloplasts tend to heal via encapsulation by connective tissue. There is often minimal to no new bone formation. In intrabony defects, grafting materials increase clinical attachment vs. open flap debridement procedures alone. However, grafting materials are not necessarily required for GTR when using an appropriate adapted periodontal membrane.

GTR Membranes
Membranes should be biocompatible, exclude unwanted tissue, integrate with tissue, maintain space, maintain barrier, stabilize the clot, and protect newly forming bone. Periodontal membranes are required for GTR procedures. GTR membranes stabilize the clot in the bony defect, prevent apical...
downgrowth of the gingival connective tissue and epithelium (exclusion), and control cell/tissue populations.

During wound healing, a fibrin clot forms and links to the root surface. Maintenance of this clot with a GTR membrane allows for new tissue attachment by allowing PDL and bone cells, with regenerative potential, to enter the wound first. If the fibrin clot is disrupted, long junctional epithelium will result. Clot formation and wound stabilization are essential for regeneration.

Membranes can be divided into 1) synthetic nonresorbable membranes, 2) synthetic resorbable membranes, and 3) natural biodegradable membranes. Synthetic nonresorbable membranes include extended polytetrafluoroethylene (ePTFE) and titanium reinforced ePTFE. An additional anesthetic episode is required to remove the ePTFE membranes in canine patients, which increases the cost of the procedure and adds additional anesthetic episodes for the patient. Furthermore, if synthetic nonresorbable membranes are exposed to the oral cavity, infection and failure can result. Synthetic resorbable membranes include polyglactin 910, poly-DL-lactide/poly-L-lactide, and polyglycolide membranes. Natural membranes include collagen and laminar bone membranes. Absorbable membranes ideally maintain physical integrity for 6–8 weeks postsurgery and are gradually resorbed thereafter.

**Complications and Recheck**
Membrane exposure is a major complication.Exposed membranes are contaminated by oral bacteria, requiring additional medical therapy or removal (particularly if synthetic nonabsorbable). Surgical site swelling, bleeding, periodontal flap perforation, and membrane exfoliation are potential complications.

At the recheck in 6 months, the site is evaluated for reattachment via light clinical probing and intraoral radiographs. However, it should be noted this assesses for reattachment (reunion of epithelial and connective tissue [gingival connective tissue, PDL, and/or bone]) and the only true way to confirm successful GTR is surgical reentry into the site for biopsy and histopathology, which is contraindicated and not performed in the clinical patient. With correct patient selection and execution of GTR, the regenerated tissue should predictably be PDL and bone and not the excluded gingival connective tissue and epithelium.

**Home Care Products and Antibiotics**
Antibiotics are never used as a monotherapy in periodontal treatment. Supragingival scaling, subgingival scaling, and periodontal surgery, in addition to exodontics as indicated, are necessary to remove the plaque biofilm, establish a clean tooth surface, reestablish normal sulcular depths, and eliminate periodontal pockets. Plaque and periodontal pockets require mechanical intervention to treat. No single pharmaceutical or chemical product will remove plaque and decrease pocket depths.

**Antibiotics**
Antibiotics are not needed in most professional periodontal cleanings involving gingivitis or mild periodontal disease. Removing the plaque biofilm and the periodontal pocket or extraction of the tooth treats periodontal infection. The use of antibiotics as a monotherapy is not a treatment. The selection of antibiotics should be chosen based on pathogens causing disease (Gram-negative anaerobes). Therefore, clindamycin, amoxicillin/clavulanic acid, and tetracyclines/doxycycline (in appropriate-aged animals and in certain conditions) are good choices. Overuse of antibiotics in pets and people leads to bacterial resistance, and we have a professional responsibility to use antibiotics correctly and judiciously.

**Home Care Products (Dentifrices)**
No home care product is a monotherapy for periodontal disease caused by the plaque biofilm. Home care products are not a substitution for a professional periodontal cleaning. General anesthesia, complete oral examination and assessment, and professional periodontal cleaning are necessary to treat
the oral cavity, whereas home care products help prevent and slow the return of plaque. The plaque biofilm and the host inflammatory response are the cause of periodontal disease. Even with meticulous home care, anesthesia for complete oral examinations (detection of tumors, periodontal pockets, fractured teeth, etc., early) and subgingival scaling is necessary throughout the life of the patient.

The list of home care products and over-the-counter products is extensive and constantly changing with new additions and deletions to the market. Some make claims and exacerbate clients’ fears of anesthesia required for dentistry. Many simply control halitosis and do not address the cause of periodontal disease - the subgingival plaque biofilm. All dental and oral surgical patients can be safely anesthetized with proper preanesthetic planning, multimodal anesthesia, patient monitoring and support, and/or referral to a veterinary dentist and veterinary anesthesiologist when indicated.

A good way to determine if a product or diet meets its label claims is to look for the Veterinary Oral Health Council (VOHC) seal. To learn more about the VOHC and how it evaluates veterinary dental products, visit www.avdc.org. The VOHC does not conduct testing. The VOHC reviews results and data voluntarily submitted by the manufacturer.

Home Care
Home care should be started prior to the establishment of periodontal disease. Home care is best started in the puppy and kitten in order to train them to accept oral care. However, many animals can be trained to accept home care after oral infection and pain have been treated. Home care is not a substitute for necessary professional assessment, intraoral radiographs, and treatment. If periodontal disease is present, it is necessary to first anesthetize the patient, assess the oral cavity with periodontal probing and intraoral radiographs, treat disease (extractions, periodontal surgery, etc.), and establish the oral cavity to a new normal baseline. Then a home care plan can be developed for the individual patient.

Home Care Product Disclaimer
The following is a list of different categories of products. It is not a comprehensive list or a list to recommend one product over the other. Each dentifrice category of product has pros and cons. The individual practitioner must read the product claims and published research in order to choose an appropriate combination of home care products and plans for each individual patient based on the client’s willingness to commit, the patient’s overall health status and medical restrictions, and the patient’s compliance with home care.

Toothbrushing
Daily brushing with a soft-bristled nylon toothbrush is the most effective method of plaque control. The soft bristles mechanically remove the plaque biofilm. However, it should be noted it is often difficult for owners to reach all areas of the mouth. Particularly, the distal maxillary and mandibular molars and the lingual/palatal sides of the dentition may be missed. The bristles may help remove plaque 1–2 mm into the gingival sulcus with appropriate techniques. Therefore, active periodontal disease and periodontal pockets require professional treatment under anesthesia to reestablish normal sulcular measurements to help allow brushing to be effective. Additives to pet toothpastes are used to increase palatability, augment the normal salivary protective systems, and provide chemical control of plaque.

Mechanical Cleansing (e.g., Diets and Chews)
There are a variety of dental chews that help control plaque and calculus. They are often designed to encourage chewing so the tooth can be mechanically scrubbed. Some products have the addition of different chemical antiplaque compounds and chemicals to bind the volatile compounds causing halitosis. Extremely hard chew toys (e.g., cow hooves, nylon bones, bones, ice cubes) commonly fracture teeth, leading to endodontic disease and hidden periapical infections.
There are veterinary prescriptions dental diets that control plaque through fiber arrangement that mechanically clean the teeth as the pet chews through the kibble. If the pet has no chewing teeth remaining in the mouth, or does not chew the food, then diets or chews will not be effective dentifrices.

There are diets and chews with the addition of polyphosphates that control calculus accumulation by binding the salivary calcium carbonate and calcium phosphate salts in the saliva and thereby prevent some mineralized deposits (calculus) on the teeth.

**Chemical Antiplaque Products**
There are 0.1% chlorhexidine acetate and 0.12% chlorhexidine gluconate oral rinses that can be used on a daily basis. Chlorhexidine is a cationic bis-biguanide that disrupts bacterial cell wall lipoproteins and precipitates the bacterial cytoplasm. It can bind to the pellicle and has a prolonged effect. It can be inactivated when interacting with other oral product compounds. These agents help control plaque but do little to slow the accumulation of calculus.

Zinc-containing products (zinc ascorbate, zinc gluconate) may help control plaque. Their mechanism is an antibacterial effect. They may also bind volatile sulfur compounds that cause halitosis.

Xylitol is a sugar alcohol incorporated in many human dental products and gum for its anti-caries effects. It has been incorporated into various drinking water additives for pets. It should be noted that acute, life-threatening hypoglycemic episodes and hepatic necrosis have been reported in dogs consuming human products containing xylitol. Careful review of manufacturer safety studies, peer-reviewed literature, efficacy studies, poison control center data, and individual patient susceptibility should be investigated by the veterinarian regarding veterinary products containing xylitol.

Other products including cetylpyridinium chloride, thymol, sodium fluoride, triclosan, quaternary ammonium, phenol, sodium lauryl sulfate, sanguinaria, povidone-iodine, herbal compounds, eucalyptol, methanol, eugenol, etc., have been used in humans. These compounds are discussed in the human literature.

**Enzyme Systems**
Enzyme systems are often added to pet toothpastes and dental products. Common enzymes are glucose oxidase and lactoperoxidase that react with oxygen and water in the oral cavity to form hypothiocyanite (an endogenous salivary product shown to have antibacterial effects).

**Dental Surface Barrier Sealants/Treatments**
Inert polymer sealants applied to teeth following a periodontal cleaning and at home are designed to form an electrostatic bond to the tooth enamel. Once bound, they are designed to provide a hydrophobic barrier that diminishes attachment of plaque and stain.

**Natural Water Additive**
A recent natural water additive for dogs to help control plaque received VOHC approval. A combination of natural antibacterial products, antioxidants, and natural preservatives are included in the formulation.

**Host Modulation**
Host modulation is an emerging treatment for human periodontal disease. Once again, it is not a substitute for professional subgingival periodontal cleanings and treatment. Rather, it helps address the inflammatory response to the plaque biofilm. The discussion of this topic is beyond the scope of an introductory lecture.

**Conclusion**
Periodontal disease is in your practice every single day. Our veterinary patients are suffering silently from chronic infection and pain. Expansion of your dental services to treat periodontal disease will benefit your patients, satisfy your clients, and improve the health of your practice. Implementing a
home care plan in veterinary patients begins prior to the establishment of periodontal disease in young patients or after a professional periodontal cleaning and examination in patients with established periodontal disease. Each patient is an individual, and different patients will require different treatment plans depending on behavior, remaining teeth, underlying medical conditions, compliance of owner, compliance of pet, etc. Daily toothbrushing is the gold standard. However, even with meticulous home care, anesthetized comprehensive oral examinations, intraoral radiographs, and periodontal cleanings will be necessary throughout the patient’s life.

REFERENCES

References are available upon request.
Feline Tooth Resorption: Practical Approaches
Kevin S. Stepaniuk, DVM, FAVD, DAVDC
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INTRODUCTION
Tooth resorption is a common and frustrating dental problem in the feline patient. It has been known previously by many names. The accepted AVDC nomenclature term is tooth resorption. The prevalence of the disease, in cats, has been reported in the literature as 20–75%.

PATHOPHYSIOLOGY
The lesions begin in the cementum and can occur anywhere on the root surface and not just the cervical region. The resorption progresses into the dentin and enamel of the tooth root and crown. Clinically, these teeth may have localized gingival enlargements of highly vascularized, inflamed granulation tissue covering supragingival defects, small defects at the gingival margin, and/or no supragingival lesions. Intraoral radiographs are required to diagnose and treat the disease. These lesions are painful, but, as with all dental and oral disease, the range of clinical signs can vary from partial anorexia, weight loss, halitosis, ptyalism, dysphagia, etc., to no obvious clinical signs at all. If the lesions remain below the gingival attachment, they are often asymptomatic since the dentin tubules and pulp are not exposed to the oral environment. Some cats may exhibit supereruption of involved teeth (particularly the canine teeth) to potentially maintain a normal biological width. These supererupted teeth are associated with hypercementosis. The increased exposure of the tooth root needs to be differentiated from gingival recession/root exposure that is caused by periodontitis.

The cause of tooth resorption is not fully understood. Odontoclasts are derived from hematopoietic stem cells. These multinucleated cells resorb mineralized tooth structure on several regions of the root simultaneously. The stimulation of the odontoclasts is not known. Abfraction, diet, minerals, water sources, periodontal disease and inflammation, and most recently vitamin D have been speculated as inciting causes. A current publication challenges the vitamin D hypothesis. Vasodentin, a type of dentin with tubules positioned randomly and communicating with the pulp canal, has been observed. The micro-hardness and thickness of feline enamel may be a factor. Furcation canals and lateral canals may or may not play a role. The initial lesions are noninfectious and noninflammatory. There may or may not be breed predilections. There is no sex predilection. The lesions may very well be multifactorial. Essentially, feline tooth resorption not associated with infection (periodontal or endodontic disease) is classified as idiopathic.

DIAGNOSIS
The diagnosis of tooth resorption requires clinical examination and intraoral radiographs while the patient is anesthetized. Without intraoral radiographs, diagnosis and treatment plans cannot be accomplished.

The stage of lesions can be classified by the extent of tooth involvement (see AVDC Nomenclature www.avdc.org):

- **Stage 1 (TR1):** Mild dental hard tissue loss (cementum or cementum and enamel)
- **Stage 2 (TR2):** Moderate dental hard tissue loss (cementum or cementum and enamel with loss of dentin that does not extend into the pulp cavity)
- **Stage 3 (TR3):** Deep dental hard tissue loss (cementum or cementum and enamel with loss of dentin that does extend into the pulp cavity)
- **Stage 4 (TR4):** Extensive dental hard tissue loss (cementum or cementum and enamel with loss of dentin that does extend into the pulp cavity; most of the tooth has lost its integrity)
- **TR4a** (crown = root), **TR4b** (crown > root), **TR4c** (crown < root)

- **Stage 5 (TR5):** Remnants of dental hard tissue are visible only as irregular radiopacities, and gingival covering is complete

The lesions can be further divided into types. It is a requirement to utilize intraoral radiographs in order to determine the type of TR and therefore develop the treatment plan. **Type 1** tooth resorption will have normal root opacity with a surrounding lamina lucida and usually a definable root canal. There may be associated periodontal or endodontic disease. With **Type 2** (replacement resorption), the teeth have undergone significant resorption and have opacity more similar to the surrounding alveolar bone. There is loss of the lamina lucida, and dentoalveolar ankylosis is present. There may be no discernible root structure present. **Type 3** occurs when one root is Type 1 and one root is Type 2. It is essential that the surgeon use intraoral dental radiographs and understand Type 1, Type 2, and Type 3 lesions for treatment planning. Diagnosis requires anesthesia, a clinical exam, the use of a dental probe and explorer, and full-mouth intraoral dental radiographs.

**TREATMENT**

The current treatment recommendation is for extraction of stage 2–4 tooth resorption lesions. All teeth with Type 1 lesions must be extracted. Type 2 lesion teeth may be treated with subgingival crown amputation and intentional root retention (see www.avdc.org position statement), but I extract most teeth and reserve subgingival crown amputation for select cases. Unfortunately, many veterinarians perform subgingival crown amputations incorrectly or when they are contraindicated. Examples of incorrect treatment include, but are not limited to, amputating after having difficulty extracting the tooth; performing root “pulverization/atomization;” crown amputations without intraoral dental radiographs; performing subgingival crown amputation incorrectly, resulting in retained, infected, sequestrated roots causing chronic pain and infection. My general rule is to extract, extract, extract, and only perform subgingival crown amputations when all the following criteria are met. If all the rules are followed correctly, there is a good success rate for subgingival crown amputations.

**Subgingival crown amputation with intentional root retention criteria:**

1. Intraoral radiographs utilized.
2. Roots must show Type 2 replacement resorption.
3. There are no periapical lucencies (endodontic disease).
4. There is no periodontal disease.
5. The patient does not have “stomatitis.”
6. The owner must be advised that subgingival crown amputation was performed and roots were intentionally left.
7. It must be recommended to recheck the sites with intraoral radiographs in 6–12 months.
8. The procedure is clearly noted in the medical and dental record.
9. The tooth was amputated from the start and was not amputated because of a failed extraction attempt.

Regardless if the teeth are extracted or crown amputated, patients are treated perioperatively with multimodal analgesia protocols and discharged with analgesics. All surgical sites are sutured closed with absorbable suture, such as poliglecaprone-25, chromic gut, or polyglactin 910. Antibiotics are used postoperatively for 7–10 days in cases with significant periodontal disease or extensive surgical flap exposure of the maxillary and mandibular bone.
Extraction

“Extractions” are surgical procedures requiring significant training and skill. Surgery is defined as the treatment of disease, injury, or deformity by manual or instrumental operations, as the removal of diseased parts or tissue by cutting. Extraction is defined as the process or act of pulling or drawing out. In order to correctly “extract” teeth in veterinary patients, surgery must be performed. “Extractions” are oral surgery and should be treated as such. Veterinarians perform “extractions.” The ultimate goal should be for a pain- and infection-free oral cavity in our patients.

The majority of extractions in veterinary dentistry are surgical extractions (creation of a mucoperiosteal flap and removal of bone), except for extraction of incisors and some premolars. Extractions involve the creation of mucoperiosteal flaps, removal of bone, sectioning of multirooted teeth, curetting the alveolus of infection, smoothing the bone (alveoloplasty and/or osteoplasty), suturing the extraction site closed, and postoperative care. The American Veterinary Dental College position statement is that treatment planning and exodontics should be performed only by a veterinarian (www.avdc.org). All extraction treatment planning requires intraoral dental radiography.

Armamentarium

In order to be successful and to be professionally satisfied performing extractions, the following equipment, but not limited to, is recommended:

1. Protective masks, glasses, and gloves
2. Good lighting
3. An ergonomic work environment
4. Magnification (if possible)
5. Scalpel blades (#15, #15c, #11)
6. Scalpel handle (I prefer a round scalpel handle)
7. Water-cooled, high-speed handpiece - to prevent thermal necrosis of bone
8. Dental burs (such as #330, #331, #1/2, #1, #2, #4, #669, #701, or a bur of your choice and a medium or fine diamond bur)
9. Dental periosteal elevators
10. Dental luxators
11. Dental elevators
12. Extraction forceps
13. Root tip picks
14. Excavators (to clean out the alveolus)
15. Tissue forceps
16. Needle holders
17. Absorbable suture (4-0 or 5-0 poliglecaprone 25, 4-0 or 5-0 chromic gut, 4-0 or 5-0 polyglactin 910 (Vicryl®-Rapid™)) on a P-3 needle
18. Tongue depressor
19. Minnesota retractor
20. All instrumentation used delicately and with control - A finger stop should be near the tip of the working instrument to stop the instrument if it slips
21. Patience!

The General Technique (Single-Rooted Teeth and Individual Roots After Sectioning)

Client consent is obtained for the extraction. The goal is to remove the entire tooth from the alveolus with minimal trauma to the surrounding bone and tissue. The periodontal ligament attaches to the tooth and the alveolar bone in order to hold the tooth in the mouth. The ligament is designed to withstand short bursts of pressures/forces. The ligament must be fatigued in order to remove the tooth. Extracting the tooth is about patience and finesse, not brute force.
**Extractions**

- Simple closed extraction (X):
  - Envelope flap
  - e.g., incisor tooth
- Extraction with tooth sectioning - nonsurgical (XS):
  - Sectioned multi-root tooth with an envelope flap
  - e.g., premolar and molar closed
- Surgical extraction (XSS):
  - Open - Releasing mucoperiosteal flap
  - e.g., Canine - open, premolar or molar - open, incisors - open

The oral cavity is rinsed with an oral 0.12% chlorhexidine gluconate solution. All the surgical procedures are clean contaminated; sterilized surgical instruments and dental burs should be used. Intraoral radiographs are always obtained for treatment planning. An intrasulcular or parasulcular incision is made to release the gingiva by cutting the junctional epithelium and connective tissue. A mucoperiosteal flap is created, if indicated. An appropriate-sized dental elevator (fits the curvature of the tooth root) is used with axial pressure to cut the periodontal ligament fibers. **A major pitfall is not placing the instrument in the periodontal ligament space, resulting in crushing of alveolar bone. This delays extraction and results in unnecessary surgical trauma.** Once the elevator is in position, rotation will cause the periodontal ligaments to stretch. Hold the position and wait (15–30 seconds). Bleeding (periodontal ligament is being damaged) should be noted. Repeat the procedure and use a smaller elevator/luxator that fits the curvature of the root as you work apically. Repeat again as needed. Take time to fatigue the ligament and damage the periodontal ligament fibers.

Once the root is sufficiently mobile, and only when it is mobile, do you reach for the extraction forceps. The tooth then can be grasped with extraction forceps and rotated on the long axis. The whole tooth should be present. If not, take an intraoral dental radiograph and remove the retained root fragment. “Burring out” or “atomizing” retained roots is **not recommended and must not be done**, because damage to surrounding bone and neurovascular structures can occur. The retained root fragments can be retrieved with the use of root tip picks.

The alveolus is cleaned with a curette to remove granulation tissue, purulent debris, and bone fragments, and then lavaged with an oral 0.12% chlorhexidine gluconate solution. The margins of the alveolus and cortical bone are carefully smoothed with a medium diamond football-shaped bur in order to remove rough spicules of bone.

An intraoral dental radiograph is obtained to document extraction of the tooth. Most extraction sites do not require osteoconductive material. A healthy blood clot is a phenomenal osteogenic, osteoinductive, and osteoconductive material.

Surgical margins are freshened so healthy, non-epithelialized margins are opposed. Extraction sites are sutured closed.

**Key points in surgical site closure include:**
1. **No tension** of the mucoperiosteal flap
2. Suture lines over bone
3. Sutures 2 mm apart with 2 mm bites of tissue
4. No bony spicules or irregular rough bone margins beneath the mucoperiosteal flap

**Postoperative Recommendations**

Appropriate multimodal postoperative pain management is prescribed for 5–7 days. The patient should be fed soft food for 7–10 days. Appropriate antibiotics (amoxicillin-clavulanic acid or clindamycin) are prescribed for 7–10 days as indicated. A recheck of the surgical site in 10–14 days is recommended.
Extraction Complications
1. **A fractured root or root tip** is common and must be removed to complete the extraction.
2. **Intrusion of root tips** into the mandibular canal, infraorbital canal, or nasal cavity should be avoided. If intrusion occurs and the root tip cannot be safely retrieved, referral to a veterinary dentist is recommended for removal of the root tips.
3. Major neurovascular structures are in immediate proximity to, adjacent to, and/or encircling the roots of many teeth (infraorbital, palatine, mandibular, and mental neurovascular bundles). **Extensive hemorrhage** is possible if the maxillary, infraorbital, palatine, or mandibular arteries are damaged during extraction. Additionally, neuropathies are possible if the nerves are damaged.
4. **Mandibular fracture** is possible but is completely avoided with preoperative intraoral dental radiographs and proper surgical technique.
5. Slipping of surgical instruments and **orbital penetration** should not occur with proper surgical technique but has been reported.
6. **Maxillary lip entrapment** by the mandibular canine teeth following mandibular canine tooth extraction can occur in cats. Excessive buccal bone removal, tension on the flap, and conformation can potentiate the problem. If nonhealing maxillary dermal abrasions occur, crown reduction and vital pulpotomy or extractions of the offending mandibular canine tooth/teeth are necessary to resolve the complication.

**Subgingival Crown Amputation with Intentional Root Retention**
Crown amputations are reserved for clear tooth resorption with a radiographic diagnosis of Type 2 tooth resorption. All Type 1 teeth must be extracted. Type 2 lesion teeth may be crown amputated (see www.avdc.org position statement).

An envelope flap is created. A tongue depressor is used to protect the soft tissues of the tongue when treating mandibular teeth. The envelope flap is carefully lifted with a periosteal elevator to expose the furcation and marginal bone. A 330 bur is used parallel to the marginal bone to excise the marginal bone and crown. Once the crown is removed, a medium grit football diamond bur is used to continue the subgingival crown amputation ± 2 mm apically. Smooth, mesially and distally tapering bone margins should be left. An intraoral radiograph is obtained to evaluate the contour of the amputation and to be certain no bone or tooth fragments persist coronally. The site is rinsed with 0.12% chlorhexidine gluconate and sutured closed. All surgical sites are sutured closed with absorbable suture such as poliglecaprone-25, chromic gut, or polyglactin 910.

Crown Amputation Complications
1. Tearing of the gingival tissue, preventing closure. Delicate tissue handling and careful elevation are necessary to prevent the complication.
2. Incomplete crown removal, irritating the overlying gingiva. Post-op radiographs are necessary to evaluate, identify, and correct this problem.
3. Utilizing a tongue depressor to protect the tissues easily prevents laceration of the lingual tissue with the high-speed bur.
4. Root remnant infections secondary to incorrect diagnosis of tooth resorption type. Intraoral radiographs are necessary for correct diagnosis.

**References**
References are available upon request.
Intraoral Radiographic Interpretation: Making Sense Out of the Shadows
Kevin S. Stepaniuk, DVM, FAVD, DAVDC
University of Minnesota, St. Paul, MN, USA

INTRODUCTION
Intraoral dental radiographs are required in order to assess, diagnose, and treat all dental-related pathology. The majority of dental pathology occurs subgingivally, and imaging is necessary to assess for disease, diagnose disease, develop a treatment plan, and monitor treatment success. The cost of a dental radiograph generator and image capture device is cost effective and should be necessary and required medical equipment in all small animal general practices.

The indication for intraoral dental radiographs is veterinary dentistry. Dental intraoral radiographs should be obtained for, but not limited to, periodontal disease (periodontal pockets), endodontic disease (fractured teeth with or without pulp exposure, discolored teeth), missing teeth, tooth resorptive lesions, oral masses, painful teeth, pre-extraction, post-extraction, sinus tracts, fistulas, tooth developmental abnormalities, and nasal discharge. Intraoral radiographs identified 27.8% and 41.7% clinically important findings in teeth without clinical lesions in dogs and cats, respectively (Table 1). Additionally, 50.0% and 53.9% additional findings and clinically essential (22.6% and 32.2%) findings in dogs and cats with clinical lesions were identified, respectively (Table 2). (Verstraete FJ, Kass PH, Terpak CH. Diagnostic value of full-mouth radiography in cats. Am J Vet Res. 1998;59(6):692–695. - Verstraete FJ, Kass PH, Terpak CH. Diagnostic value of full-mouth radiography in dogs. Am J Vet Res. 1998;59(6):686–691.)

Table 1. Value of radiographs - no clinical findings present in the patient

<table>
<thead>
<tr>
<th></th>
<th>Dogs</th>
<th>Cats</th>
</tr>
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<tbody>
<tr>
<td>Incidental findings</td>
<td>41.7%</td>
<td>4.8%</td>
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<tr>
<td>Clinically important findings</td>
<td>27.8%</td>
<td>41.7%</td>
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<tr>
<td>Radiographs of no value</td>
<td>30.5%</td>
<td>53.6%</td>
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Table 2. Value of radiographs - clinical findings present in the patient

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Confirmation only</td>
<td>24.3%</td>
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<tr>
<td>Additional findings</td>
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<td>53.9%</td>
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<tr>
<td>Clinically essential findings</td>
<td>22.6%</td>
<td>32.2%</td>
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<tr>
<td>No value</td>
<td>3.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

DENTAL ANATOMY
Dogs and cats are diphyodont (two sets of teeth: primary [deciduous] and adult). Each tooth has a crown and a root. The apex of the root is the terminal end of the root where the neurovascular bundle enters the tooth. The cusp is the terminal end of the crown.

The tooth is composed of organic and inorganic material. The three hard (mineralized) tissues of the tooth include the enamel (crown only), dentin (root and crown) and cementum (root only). The cementum and enamel meet at the cementoenamel junction (CEJ). A tooth is a living structure, and dentin is continually produced throughout the life of an animal if the tooth remains vital. Odontoblasts produce dentin and are located in the pulp with the blood vessels, lymphatics, and nerves. The pulp
Incisors

It cementum.

The tooth is anchored in the jaws by the periodontium. The incisive bones, maxillary bone, and mandibular bone anchor the teeth.

The periodontium consists of the 1) gingiva, 2) alveolar bone, 3) periodontal ligament, and 4) cementum. Radiographically, the alveolar bone and periodontal ligament space are commonly evaluated to assess periodontal disease. Normal cementum cannot be seen radiographically, as it consists of just a few cell layers.

**DENTAL FORMULAE FOR THE DOG AND CAT**

It is necessary to understand the correct number of teeth in the dog and cat. Any missing teeth, extra teeth (supernumerary teeth), malpositioned teeth, etc., require intraoral radiographs.

**Dog**:

- Deciduous: 2 x (3I/3I, 1C/1C, 3PM/3PM) = 28
- Adult: 2 x (3I/I, 1C/1C, 4PM/4PM, 2M/3M) = 42

**Cat**:

- Deciduous: 2 x (3I/3I, 1C/1C, 3PM/2PM) = 26
- Adult: 2 x (3I/I, 1C/1C, 3PM/2PM, 1M/1M) = 30

**NORMAL CANINE AND FELINE TOOTH ERUPTION TIMES**

It is necessary to understand normal tooth eruption times. If teeth are missing or delayed in eruption, immediate intraoral radiographs are recommended. If a tooth is embedded beneath thick gingival connective tissue, intervention with an operculectomy during the window of tooth eruptive force may allow the tooth to move into the correct position. Waiting until the patient is older is too late, as no eruptive force will be left.

<table>
<thead>
<tr>
<th></th>
<th>Deciduous (weeks)</th>
<th>Adult (months)</th>
<th>Deciduous (weeks)</th>
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<tr>
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<td>Premolars</td>
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<tr>
<td>Molars</td>
<td>5–7</td>
<td></td>
<td></td>
<td>4–5</td>
</tr>
</tbody>
</table>

**DENTAL TERMINOLOGY**

Dental nomenclature can be found at the American Veterinary Dental College website (www.avdc.org).

**Modified Triadan System**

Teeth can be named by various tooth-numbering systems. The anatomical names of the teeth and the modified Triadan System are the commonly used nomenclature in veterinary dentistry. The modified Triadan System allows easier electronic medical records and can be used across veterinary species, even with morphological tooth differences between carnivores and herbivores.

- The adult right maxillary quadrant = 100; the deciduous right maxillary quadrant = 500
- The adult left maxillary quadrant = 200; the deciduous left maxillary quadrant = 600
- The adult left mandibular quadrant = 300; the deciduous left mandibular quadrant = 700
- The adult right mandibular quadrant = 400; the deciduous right mandibular quadrant = 800
The teeth are then numbered from mesial to distal, starting with the number 1. All canine teeth will end with the number “4,” and 1st molars will end with the number “9.” If teeth are missing, a gap is left in the numbering sequence. Felines are missing the first maxillary premolar. Therefore, the first teeth distal to the canine teeth are 106 and 206, right and left, respectively. Likewise, felines are missing the first two premolars in the mandibles. Therefore, the first teeth distal to the canine teeth are 307 and 407, left and right, respectively.

Anatomical Directional Terms in the Oral Cavity (www.avdc.org)

Mesial and distal are terms applicable to tooth surfaces. The mesial surface is the surface of the tooth toward the median line of the oral cavity following the curve of the dental arcade. The distal surface is the surface of the tooth away from the median line of the oral cavity following the curve of the dental arcade.

Lingual and palatal: The surface of a mandibular or maxillary tooth facing the tongue is the lingual surface. Palatal can also be used when referring to the lingual surface of maxillary teeth.

Vestibular or buccal or labial is referring to the surface of the tooth facing the vestibule or lips.

Rostral and caudal are the positional and directional anatomical terms applicable to the head in a sagittal plane in nonhuman vertebrates. Rostral refers to a structure closer to, or a direction toward the most forward structure of the head. Caudal refers to a structure closer to, or a direction toward, the tail.

**NORMAL INTRAORAL RADIOGRAPHIC ANATOMY**

Radiographs are 2-D representations of 3-D structures. Therefore, overlying structures causing summation and superimposition frequently create artifacts.

In the young patient, the dentin walls are thin, and the pulp system is large. The root will not be fully formed until apexogenesis is complete. As the tooth ages, secondary dentin production continues, the endodontic system becomes smaller, and a root is formed. There is a radiolucent structure around each tooth (lamina lucida) that represents the space of the periodontal ligament. Immediately adjacent to the lamina lucida is the lamina dura (where the periodontal ligament attaches to the alveolar bone). This structure is a radiopaque structure that loses opacity as the patient ages. The trabecular pattern of supporting bone becomes coarser and less distinct with age. The veterinarian should become familiar with normal structures (e.g., mental foramen, developmental grooves) so as not to mistake them for pathology.

Normal anatomical landmarks visualized include the radiolucent mandibular canal, mental foramen (rostral, middle, and caudal), and mandibular symphysis. Particularly, the middle mental foramen can be superimposed on the apex of the mandibular canine tooth and/or 1st and 2nd premolars and misinterpreted as pathology. When in doubt, take a second film at a different angle. If the radiolucency stays with the tooth, it is likely pathology; if it moves away, it is likely the normal foramen. In the maxilla, the nasal structures, nasopalatine foramen, and intersections between the maxillary bones are visualized.

It takes approximately 40–50% mineral loss of tooth and bone structures before radiographic changes can be visualized on the dental film or digital dental radiographic system. Therefore, radiographs underestimate the extent of bone loss and pathology and may not always correlate with acute clinical signs. Radiographs are a snapshot in time, and recheck radiographs 6–12 months following the initial radiographic image are often necessary to evaluate the progression of disease and/or healing of bone and tooth structures. Finally, radiographs are 2-D representations of 3-D structures. Therefore, overlying structures causing summation and superimposition frequently create artifacts.

**INTRAORAL RADIOGRAPH INTERPRETATION**

A light box should be available for viewing dental radiographs if a digital system is not being utilized.

1. Be certain that the film is of diagnostic quality.
2. Mount the radiographs with a labial-mounted technique for viewing.
3. Be certain the pertinent anatomy is visible for viewing.
4. Examine the entire radiograph.
5. Identify normal anatomical landmarks.
6. Examine the bone of the mandible and maxilla.
7. Examine the crown, cervical region, root, enamel, and dentin.
8. Examine the alveolar marginal bone, interproximal bone, furcation bone, lamina dura, and periodontal ligament space.
10. Interpret the radiographic findings in conjunction with the oral exam findings.
11. Record the radiographic findings (the roentgen signs) - (e.g., a periapical lucency [rarefaction] can be seen radiographically, not a periapical abscess).
12. Record the radiographic impression.

Roentgen Signs of Periodontal Disease
Radiographically, there will be loss of the marginal bone, loss of the lamina dura, widening of the lamina lucida (periodontal ligament space), and horizontal and vertical bone loss due to the resorption of bone. Horizontal bone loss occurs when the cortical supporting bone around the tooth and adjacent teeth is lost at a similar rate. If the soft tissue does not recess at a similar rate as the bone, a suprabony periodontal pocket will be formed. Vertical bone loss occurs when there is one area of bone loss around a tooth with adjacent supporting bone and mineralized tooth structures remaining more coronal. Vertical bone loss results in infrabony pockets (single-wall defect, two-wall defect, three-wall defect, and four-wall defect).

Lesions of Endodontic Origin
Endodontic disease can result in changes within and around the tooth. Fractured teeth with pulp exposure are infected and require treatment. However, trauma that does not create pulp exposure (uncomplicated crown fractures) can still lead to endodontic disease due to irreversible pulpitis, permeability of dentin tubules to oral bacteria and toxins, and root fractures.

A periapical (periapical) lucency is a classic bone change seen with endodontic disease. Additional changes in the bone can include a widened lamina lucida (particularly apically), periapical radiopacities and sclerosis, external inflammatory root resorption, and/or noncontinuous lamina dura. The tooth may have arrested development when compared to the contralateral tooth, and a wider endodontic system is evident. Additionally, pulpitis can lead to mineralization of the root canal system and narrowing compared to the contralateral healthy tooth. There may be internal resorption or external resorption present. External resorption is more common and involves inflammation causing radiolucent defects of the root (particularly the apex of the tooth). Internal resorption occurs within the endodontic system and can be radiographically discerned from external resorption by changing the angle of the radiographic beam. Internal resorption will stay with the root canal system and the normal tapering lucency and definition of the root canal system will be lost in the region of the resorption.

Radiographic lesions of endodontic origin include: no radiographic changes (early lesions), widening of the apical periodontal ligament space, loss of apical lamina dura, diffuse irregular periapical lucency, distinct periapical lucency, diffuse area of radiopacity - sclerosing (condensing) osteitis, root tip resorption, internal resorption, external inflammatory tooth resorption, arrested tooth development, and/or accelerated tooth mineralization (dystrophic mineralization, pulp obliteration).
**Feline Tooth Resorption**

Tooth resorption lesions can be divided into stages and types. Types refer to the radiographic appearance and are crucial for treatment planning. Type 1 is generally associated with periodontal disease or apical periodontitis from endodontic disease. There will be a normal root opacity with a surrounding lamina lucida and usually a definable root canal. With Type 2 (replacement resorption), the teeth have undergone significant resorption and have a different opacity/density. There is loss of the lamina lucida, and dentoalveolar ankylosis is present. There may be no discernible root structure present. These teeth are not associated with periodontitis. Type 3 is when one root is Type 1 and one root is Type 2.

**Canine Tooth Resorption**

Tooth resorption occurring in other species (e.g., dogs, humans), identified with intraoral radiographs, has been known for many years, but accurate description in dogs has been lacking in the literature despite being frequently identified. Classification of human tooth resorption is documented.

Recently, several publications have evaluated tooth resorption in dogs:


Peralta, *et al.* (2010) identified increased frequency of tooth resorption in older and large-breed dogs with no sex predilection. A population of 224 dogs with full-mouth intraoral radiographs was evaluated. Tooth resorption was detected in 53.6% of the dogs (11.1% of all teeth evaluated had tooth resorptive lesions: 8.7% external replacement resorption and 1.4% external inflammatory resorption). The human classification system could be applied to 96.3% of the affected teeth. Canine tooth resorption was a common finding. The majority of tooth resorption was external replacement resorption (34.4% of dogs) and external inflammatory resorption (25.9% of dogs).

**Radiographic and Clinical Descriptions of Types of Tooth Resorption**

- **External replacement resorption** - disappearance of the periodontal ligament space and replacement of tooth structure with alveolar bone
- **External inflammatory resorption** - loss of dental tissues and adjacent alveolar bone secondary to inflammatory conditions such as endodontic and periodontal disease
- **External cervical root surface resorption** - resorptive process starting at cementoenamel junction of the tooth that progresses coronally and apically
- **External surface resorption** - resorptive lacunae involving the cementum and dentin and not the periodontal ligament and lamina dura; the periodontal ligament remains
- **Internal inflammatory resorption** - oval-shaped irregularity within the pulp canal resulting from endodontic inflammation
- **Internal surface resorption** - apical third oval-shaped enlargement that may represent revascularization following a mild traumatic injury
- **Internal replacement resorption** - irregular enlargement with tunnel-like appearance adjacent to pulp canal
**ORAL NEOPLASIA**

In general, and with exceptions, most malignant tumors invade bone, whereas most benign lesions do not. Aggressive lesions have rapid changes, indistinct edges with multiple areas of lysis, wide reactive zones, cortical lysis, and periosteal layers of opacity. The associated teeth are usually floating in position, resulting in increased tooth mobility, and tooth resorption is irregular and may have a spiked appearance. Nonaggressive lesions tend to displace teeth, and mobility is variable. The rate of change of the bone is slow, with a well-defined area of lysis with distinct, narrow margins. A uniform periosteal reaction is present.

**REFERENCES**

References are available upon request.
Fractured Teeth (Endodontic Disease) for the General Practitioner
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INTRODUCTION
The tooth is composed of organic and inorganic material. The three hard tissues of the tooth include the enamel (crown only), dentin (root and crown), and cementum (root only). The cementum and enamel meet at the cementoenamel junction (CEJ). The cementum attaches to the periodontal ligament to the tooth. Dentin is continually produced throughout the life of an animal in a vital tooth. Dentin comprises the majority of the mineralized substance of the tooth and is comprised of 30,000–70,000 dentin tubules/mm² of surface area. Within the dentin tubules are the odontoblastic processes of the odontoblasts. The odontoblast cell body is adjacent to the dentin and comprises one of the four histological cell layers of the pulp.

The pulp (endodontic system) is divided into the root (pulp) canal (in the root), the pulp chamber (in the crown), and the pulp horns (in the cusps of the crown). The four (4) histological layers of the pulp include the odontoblasts layer, the cell free-zone of Weil, cell-rich layer, and the central neurovascular center. Odontoblasts produce primary dentin prior to tooth eruption, secondary dentin throughout life, and tertiary dentin (reactionary and reparative dentin) in response to dentin irritation. Acutely exposed dentin tubules (enamel and uncomplicated crown and crown-root fractures) and pulp (complicated crown and crown-root fractures) are painful and allow access of oral bacteria and toxins into the pulp, resulting in pulpitis. The concussive forces of trauma and/or uncomplicated crown and crown-root fractures can lead to reversible and irreversible pulpitis, depending on the extent of dentin tubular injury, dentin thickness, and nature of insult.

FRACTURED TEETH
All fractured teeth with pulp exposure require endodontic treatment or extraction. Intraoral dental radiographs for assessment and treatment are required.

Classification of tooth fractures can be found at www.avdc.org (nomenclature). Enamel infraction (an incomplete fracture of the enamel without loss of tooth substance), enamel fracture (a fracture with loss of crown substance confined to the enamel), uncomplicated crown fracture (a fracture of the crown that involves the enamel and dentin but does not expose the pulp), complicated crown fracture (a fracture of the crown that involves the enamel and dentin that does expose the pulp), uncomplicated crown-root fracture (a fracture of the crown and root that does not expose the pulp), complicated crown-root fracture (a fracture of the crown and root that does expose the pulp), and a root fracture (a fracture involving the root). Uncomplicated crown fractures may lead to the death of the tooth by translocation of bacteria and toxins across exposed dentin tubules or the force that fractured the tooth (concussive pulpitis). Complicated and uncomplicated crown-root fractures may lead to periodontal disease since the normal anatomical structures of the subgingival periodontium are altered.

DISCOLORED TEETH (LOCALIZED INTRINSIC STAINED TEETH)
Teeth may be discolored due to extrinsic stain (on the surface of the tooth) or intrinsic stain (stain inside the tooth). Generalized intrinsic staining may be secondary to congenital, pharmaceutical, genetic, and environmental problems during adult tooth development. Full-mouth intraoral radiographs are required to assess the teeth. Treatment may or may not be required for generalized intrinsic stain, on a tooth-by-tooth basis, depending on the cause.

Localized intrinsic staining is consistent with a nonvital tooth. Total or partial pulp necrosis was found in 92.2% of intrinsically stained teeth. Radiographic signs consistent with endodontic disease were absent in 42.9% of those teeth. The intrinsic stain is the result of pulpitis and pulp hemorrhage, resulting
in hemoglobin and the subsequent breakdown products in the dentin tubules. Often the patient suffers quietly in silence with only subtle clinical signs of chronic pain being noticed by an astute owner. Clients often remark the improved change in behavior following treatment of a nonvital tooth.

Treatment options include extraction (often nonstrategic teeth) or root canal treatment for strategic (mandibular and maxillary canine teeth, maxillary 4th premolars, mandibular 1st molars) and esthetic teeth (incisors). However, root canal treatment may be elected for any tooth, depending on the purpose of the patient and the client’s desires.

**INTRAORAL RADIOGRAPHIC SIGNS OF ENDODONTIC DISEASE**
A periradicular (periapical) lucency is a classic bone change seen with endodontic disease. Additional changes in the bone can include a widened lamina lucida (particularly apically), periradicular radiopacities and sclerosis, external inflammatory root resorption, and/or noncontinuous lamina dura. The tooth may have arrested development when compared to the contralateral tooth, and a wider endodontic system is evident. Additionally, pulpitis can lead to mineralization of the root canal system and narrowing compared to the contralateral healthy tooth. There may be internal or external inflammatory tooth/root resorption present. External inflammatory root resorption is more common and involves inflammation causing radiolucent defects of the root (particularly the apex of the tooth) with adjacent periodontal bone loss. Internal inflammatory resorption occurs within the endodontic system and can be radiographically discerned from external resorption by changing the angle of the radiographic beam. Internal resorption will stay with the root canal system and the normal tapering lucency, and definition of the root canal system, will be lost in the region of the resorption.

In summary, radiographic lesions of endodontic origin include: no radiographic changes (early lesions), widening of the apical periodontal ligament space, loss of apical lamina dura, diffuse irregular periapical lucency, distinct periapical lucency, diffuse area of radiopacity - sclerosing (condensing) osteitis, external inflammatory root tip resorption, internal inflammatory resorption, external inflammatory tooth resorption, arrested tooth development, and/or accelerated tooth mineralization (dystrophic mineralization, pulp obliteration).

**EXTRACTION**
Endodontically infected teeth require exodontic treatment or endodontic treatment. If the client does not elect endodontic treatment, if the patient signalment and concurrent disease processes preclude endodontic treatment, or if the tooth cannot be maintained with endodontic treatment, extraction is indicated.

**DENTAL SEALANTS/RESINS**
There are some discussion and controversy when to “seal” uncomplicated crown fractures and enamel fractures. Exposed pulp (complicated crown fractures) is not sealed. Exposed pulp requires endodontic or exodontic treatment.

With enamel and uncomplicated crown fractures, the vital tooth (odontoblasts) can occlude the dentin tubules with mineral during a process of reversible pulpitis. As with all assessments, intraoral radiographs are required. Dental sealants are recommended with known acute uncomplicated fractures exposing the dentin tubules in young animals (< 18–24 months of age). By sealing the dentin tubules 1) the dental pain from the exposed odontoblastic processes can be controlled, and 2) the translocation of bacteria and oral solutions resulting in pulp necrosis can be prevented. The sealing of older, uncomplicated crown fractures in older teeth and animals without known recent fractures remains controversial and lacks good scientific evidence to justify the treatment and associated expense.
**Total Pulpectomy (Root Canal Treatment) - Normograde Endodontics**

The dental discipline of endodontics is a broad topic. The different methods to prepare, sterilize, and obturate the various sizes and shapes of root canal systems are extensive. In veterinary endodontics, the variation of species, canal shapes, canal sizes, and tooth morphology make veterinary endodontics both fun and challenging. These notes are not meant to be comprehensive, and the reader is referred elsewhere for broader information. Veterinary endodontic procedures are not simple. It is a tactile discipline that requires training and experience as well as a consistent caseload to maintain the skills to deal with the anatomical variations that are presented. The veterinarian must first understand the basic principles of endodontics, endodontic complications and challenges, and the use of basic instrumentation (hand file and cold gutta percha techniques). Many hours of lectures and labs and additional specimen training, etc., are necessary prior to attempting root canal treatment on a patient. Additionally, there is significant expense of equipment and supplies (with expiration dates that must be respected).

**Basic Concepts of Normograde Endodontic Treatment**

Preparation of the canal includes mechanical and chemical removal of pulp, bacteria, dentin, and toxins while shaping the canal for a 3-dimensional obturation. The veterinarian must learn various techniques to clean, prepare, and obturate a canal. In fact, many techniques can be combined to disinfect, shape, and obturate the endodontic systems of veterinary species. There are endodontic studies testing the various instrumentation and obturation techniques. Dye-leakage studies, which may not correspond to clinical outcome, are used to test the various materials. It should be noted that one technique in the hands of a skilled individual might be clinically successful, whereas in the hands of another may be disastrous. Technology allows us to increase efficiency and effectiveness of endodontic procedures. However, the experienced veterinary dentist needs to be familiar with several techniques, as one technique may not be ideal for every situation. There is no “perfect system” for every patient and every case. There are positives and negatives of each technique, and the veterinary dentist should have more than one approach to resolve an endodontic challenge.

**Instrumentation and Sterilization**

Prior to cleaning the canal (instrumentation and sterilization), a proper straight-line access to each root canal system is necessary. The access points of all 42 dog teeth and 30 cat teeth are beyond the scope of these notes. Instrumentation with hand files (Hedstrom files, K-files, and K-reamers) is necessary to mechanically clean and shape the canal. Diseased pulp tissue and dentin are removed. The canal is shaped to enhance chemical disinfection and irrigation and to accept obturation materials. There are various rotary mechanical endodontic systems available and tested to enhance the cleaning and shaping of the canals.

**Endodontic Irrigation**

For wound management, surgeons often teach the “solution to pollution is dilution.” This statement can apply to endodontic irrigation. Copious irrigation (20–60 ml) with any endodontic technique is recommended in order to supply sufficient active solutions to the canal and remove the debris from the canal. There are a variety of irrigants available (17% EDTA, sodium hypochlorite [NaOCl], MTAD, hydrogen peroxide, chlorhexidine, and others). Irrigants lubricate the canal, dissolve vital and nonvital organic tissue, disinfect the canal, and remove inorganic material and the smear layer. No single irrigant can accomplish all these tasks. The canal must be instrumented to at least ISO 25 for delivery of the canal irrigants. 1) 0.1–0.2% chlorhexidine has been used. It disrupts the cell membranes of bacteria and binds to dentin. However, it is reported to be less effective than NaOCl as a disinfectant. It does not dissolve organic material. 2) NaOCl is a popular and tested canal irrigant and is the most commonly used irrigant. Disinfection relies on hypochlorous acid (HOCl) that oxidizes bacterial enzyme sulfhydryl groups.
resulting in bacterial death. NaOCl dissolves organic material when used at a minimum of 1%. However, organic materials rapidly deplete the availability of free chlorine ions necessary for bactericidal activity. Therefore, frequent replacement and exchange of the irrigant is necessary in addition to prolonged intracanal contact time. Concentrations of 0.5–5.25% have been utilized. The higher concentrations are more tissue toxic (destroys vital tissue) but provide greater organic material dissolution. NaOCl does not penetrate well into the dentin tubules when a mineralized smear layer is present, and NaOCl has poor wettability. 3) EDTA (17%) dissolves inorganic material, removes the mineralized portion of the smear layer, and opens up dentin tubules. The decalcifying effect is self-limiting; therefore, once again, liberal and copious amounts of irrigant are necessary to maintain effectiveness.

Irrigants are delivered via endodontic needles. It is estimated the irrigant does not travel farther than 1 mm from the tip of the needle. These needles are rarely long enough to reach the apical portion of a dog canine tooth. Endosonics to warm and move the irrigants (cavitation and acoustic streaming) are being utilized. Alternatively, a negative-apical-pressure system (Endovac®) is available. Endodontic vacuum systems are utilized to deliver irrigants to the most apical extent of the root canal system. Volumes of 60–100 ml of NaOCl and 20 ml of EDTA have been suggested.

Obturation

Endodontic Sealants
Prior to obturating the root canal system with gutta percha, an endodontic sealant is necessary to seal the dentin tubules. Zinc oxide-eugenol, resin-based sealants, and calcium hydroxide-based sealants are often used. Each category has pros, cons, indications, and contraindications depending on the anatomy, disease process, obturation technique to be chosen, and sealant delivery system. Once again, knowledge of all these products and having multiple products in the endodontic arsenal in the practice are necessary.

Gutta Percha Obturation
After the canals are cleaned, shaped, disinfected, dried, and sealed, the canal is filled with gutta percha. Standard gutta percha cones, using vertical and lateral condensation techniques, with various-sized pluggers and spreaders, are the traditional method and starting point for root canal treatment. To improve obturation and obtain a “hermetic seal” of the canal, various other modified techniques have been developed.

Touch ‘n Heat Warm Vertical/Lateral Compaction
Essentially, cold gutta percha is placed in the canal and heated with a Touch ‘n Heat® or System-B® heater. As the gutta percha is heated and condensed, additional cones are inserted and repeated. This technique can be used with β-gutta percha or in a technique called modified SuccessFil® (α-gutta percha) - often used in large canines with wide endodontic systems. In the latter, the apical portion is obturated with the α-gutta percha. The β-gutta percha is then inserted and heated. The warmed gutta percha is condensed with spreaders and pluggers.

GuttaFlow®
The product is a combination of gutta percha (< 30 μm), polymethyl siloxane sealer, and nano-silver particles. Compared to heated gutta percha techniques that result in shrinkage during cooling, GuttaFlow® has shown up to 0.2% expansion with setting. It allows for a 3-dimensional fill, as it is less viscous under pressure (thixotropic). The material can be forced into small canals and dentin tubules. It is reported as biocompatible and nontoxic when extruded from the apex. Several capsules may be necessary for a canine patient, increasing the cost.
**RESTORATION OF THE TEETH AND ACCESS SITES**

Restoration of the endodontic access sites and fracture sites with appropriate restoration techniques completes the procedure. Restoration and restorative materials are a large discipline, which must be understood to complete the final step of the endodontic procedure.

**SURGICAL ENDODONTICS**

Surgical endodontics is not the solution for all failed endodontic procedures. If re-instrumentation, disinfection, and obturation of a poorly performed or problematic endodontic procedure can resolve the endodontic lesion, then standard endodontics should be considered first. Additionally, two-stage endodontic procedures should also be considered prior to electing a surgical endodontic procedure when presented with chronically infected canals or open apices. Indications for surgical endodontics include failed-skillfully performed standard root canal treatment, procedural blockage that cannot be resolved, open apex (apexogenesis, apexification, apical stop, and/or normograde apical mineral trioxide aggregate [MTA®] placement is not possible), apical fenestration, periradicular drainage, or damaged, severely infected apex requiring removal and debridement. The objective is to remove severely damaged apical and periapical tissue and seal the endodontic canal with a retrograde filling. The commonly treated teeth are the canine and carnassial teeth in the dog.

**PARTIAL CORONAL PULPECTOMY AND DIRECT PULP CAPPING (VITAL PULPOTOMY)**

Vital, freshly fractured young teeth may be treated with a vital pulpotomy procedure, which is less invasive compared to surgical extraction or total pulpectomy (root canal treatment). The treatment will allow the tooth to remain vital, develop additional secondary dentin, and provide time for closure of the apical region of the tooth. A partial coronal pulpectomy with a sterile, small, round fine diamond bur is used to carefully remove the coronal pulp. A sterile paper point is applied to control hemorrhage. A direct pulp capping material called mineral trioxide aggregate (MTA®) is placed. A final restoration of glass ionomer and composite is used to restore the tooth. The restoration is finished and polished. The patient is treated with antibiotics and antiinflammatories and is scheduled for a recheck of tooth vitality with intraoral radiographs in 6–12 months and annually thereafter.

Often a young tooth (< 18 months) is fractured and there is pulp exposure. Young teeth have less secondary dentin and large endodontic systems. They may not have a completely formed root and closed apex, which preclude root canal treatment. Therefore, treatment options to save the tooth include a partial coronal pulpectomy with direct pulp capping (vital pulpotomy [VP]), apexogenesis (guided continued maturation of the root apex), or apexification (apical hard tissue barrier establishment, if the tooth is nonvital). If the owner is not interested in endodontic procedures, the tooth needs to be extracted. Arbitrary times for intervention and treatment, in relation to the complicated crown fracture, have been suggested. Obviously, the sooner the tooth is treated, the better. If the patient is < 12 months of age, a VP/apexogenesis should be performed as soon as possible but at least within 2 weeks, if the tooth is still vital. If the patient is 12–18 months of age, a VP in 1–2 days is recommended. Arguably a root canal treatment could be done in this age group if the apex is formed. The owner is always advised that followup and root canal treatment may be necessary in these teeth, as statistically many teeth may die and require root canal treatment in the future. The patient will suffer quietly in silence and, therefore, annual intraoral radiographic evaluation is recommended.

**CROWN-ROOT FRACTURES**

Crown-root and root fractures may require periodontal surgery in order to save the tooth. Additionally, these teeth may die, become discolored and infected from the same trauma (concussive pulpititis) that fractured the tooth, even if the pulp is not exposed. Intraoral radiographs, monitoring, and/or treatment are necessary.
REFERENCES
References are available upon request.
Successful Step-by-Step Oronasal Fistula Repair in Your Practice the First Time
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INTRODUCTION
An oronasal fistula (ONF) is a communication between the oral and nasal cavity. The epithelial surfaces of the nasal and oral cavity communicate via the fistula. The nasal cavity is normally separated from the oral cavity by the incisive, maxillary, and palatine bones; the associated overlying mucosa; as well as the soft-palate tissues caudally. In the caudal region of the canine nasal cavity, a maxillary recess is present and communication of the distal root of the third premolar (in some breeds), 4th premolar, and molar result in an oroantral fistula. The etiology of ONF can include periodontal disease, trauma, traumatic malocclusion (i.e., linguoversed mandibular canine teeth), electrocution, cleft palates, neoplasia, severe eosinophilic granulomas, and surgical dehiscence secondary to inappropriate, or lack of, closure of surgical extraction sites, or maxillofacial surgery.

Commonly, and for the purpose of the following discussion, oronasal fistulas secondary to severe periodontal disease and particularly, loss of the maxillary canine teeth will be discussed.

ORONASAL FISTULA SECONDARY TO PERIODONTAL DISEASE
Commonly the loss of the maxillary canine teeth and/or periodontal disease associated with the maxillary canine teeth in small-breed dogs results in oronasal fistulas. The palatal aspects of the maxillary canine teeth are separated from the nasal cavity by 1–2 millimeters of bone and nasal epithelium. Intrabony pockets (vertical bone loss) on the palatal aspects of the maxillary canine teeth (teeth 104 and 204) provide a good environment for periodontal pathogens to proliferate with resulting loss of periodontium secondary to the inflammatory response and bacterial toxins. The inflammation and infection continues, resulting in a communicating tract between the oral cavity and nasal cavity. The teeth may, or may not, be mobile, and it is not uncommon to have normal or slightly increased to moderate buccal periodontal probing measurements with very large probing depths palatally. Occasionally a trickle of blood may be seen exiting from the ipsilateral nares when the probing depths are measured palatally, helping to confirm an ONF. However, subgingival calculus and inflammatory tissue may prevent larger periodontal probing depths. The depth of the periodontal pocket may be underestimated.

Oral stratified keratinized squamous epithelium and the nasal stratified cuboidal to nonciliated pseudostratified columnar and ciliated pseudostratified columnar epithelium line the maxillary and nasal sides of the defect, respectively. An ONF allows connection of these epithelialized surfaces. Oral bacteria, food, fluid, debris, etc., communicate between the oral and nasal cavities via the epithelial-lined fistula. The nasal cavity is not designed to withstand the insults of products from the oral cavity - acute and chronic rhinitis, infection, and morbidity results. Clinical signs may include chronic nasal discharge (serous, mucopurulent, and/or epistaxis). Sneezing may or may not be present. Oronasal fistulas may be obvious upon clinical examination or may be a pinpoint lesion that requires anesthesia and a thorough oral exam to identify. Although the value of intraoral radiographs is well documented and necessary for all aspects of veterinary dentistry, in the case of an oronasal fistula on the palatal aspect of the maxillary canine teeth, intraoral radiographs often cannot easily identify the bone defect due to the summation of bone and tooth structures on the 2-dimensional radiograph. However, intraoral radiographs should always be obtained and used with clinical examination findings and periodontal probing depths to make the diagnosis.
**ARMAMENTARIUM**

In order to be successful and to be professionally satisfied performing oronasal fistula repair, the following equipment, but not limited to, is recommended:
1. Protective masks, glasses, and gloves
2. Good lighting
3. An ergonomic work environment
4. Magnification (if possible)
5. Scalpel blades (#15, #15c)
6. Scalpel handle (round scalpel handle preferred)
7. Water-cooled, high-speed handpiece
8. Dental burs (such as #330, #331, #2, #4, a medium or fine football-shaped and cylinder diamond burs)
9. Dental periosteal elevators
10. Tissue forceps
11. Needle holders
12. Absorbable suture (4-0 or 5-0 poliglecaprone 25, or 4-0 or 5-0 polyglactin 910 on a P-3 needle)
13. Tongue depressor
14. Minnesota retractor
15. All instrumentation used delicately and with control
16. Intraoral dental radiology
17. Patience!

**ONF REPAIR TECHNIQUES**

There are various techniques to repair defects between the oral and nasal cavities. Repair techniques for oronasal fistula and cleft palate defects have been reported and include single buccal mucoperiosteal sliding flap, palatal inverted and buccal sliding flaps, palatal and labial buccal pedicle flaps, split U-flap, rotational palatal flaps, auricular cartilage grafts, advancement flaps, alloplastic membrane grafts, and obturators. Advanced surgical techniques for complicated cleft palates (acquired or congenital) are discussed elsewhere. For oronasal defects secondary to periodontal disease of teeth 104 and 204, a single buccal mucoperiosteal flap is adequate for primary repair if performed correctly during the first repair procedure. It is the author’s experience that the majority of oronasal fistulas secondary to periodontal disease in the maxillary teeth can be easily closed with a single buccal mucoperiosteal flap if surgical principles are followed. With very large defects or failures, an inverted double palatal and buccal sliding flap may be utilized to close the defect. Rarely, if ever, are other more advanced techniques or grafts needed for an ONF secondary to periodontal disease of the maxillary canine teeth.

**SURGICAL PRINCIPLES FOR SUCCESSFUL FLAP REPAIR**

1. The surgical flap should be larger than the bone defect to be repaired (1.5–2.5 times the width of the anticipated bone defect). This requires planning the surgical flap for closure prior to the first incision.
2. Suture lines should be placed over bone.
3. The epithelial margins of the defect must be debrided.
4. There must be no tension on the flap.
5. The sutures should be placed 2 mm apart with 2-mm bites of tissue.
6. Gentle tissue handling.
7. Appropriate home care instructions.
8. Client and patient compliance.
**Single Buccal Full-Thickness Mucoperiosteal Flap**

The keys to surgical success, whether closing a defect or following extraction of a canine tooth with an oronasal fistula, include a large, broad-based, full-thickness (soft tissue and mucoperiosteum) mucoperiosteal flap maintaining blood supply; absolutely no tension; suture lines placed over bone; and simple-interrupted sutures placed 2 mm apart with adequate “bites” into healthy palatal tissue and mucoperiosteal flap tissue. The periodontal flap also creates visibility of the underlying bone and root surface by surgically separating gingiva or mucosa from the underlying tissues. Visualization of the bone defect into the nasal cavity is necessary to debride any necrotic bone margins, remove the inflammatory tissue, and remove the communicating epithelium. The goal of surgical intervention is to provide an epithelial surface on the nasal and oral sides of the flap but removal of all the communicating epithelial with connective tissue margins apposed during the surgical closure. Nasal epithelial cells will migrate over the nasal side of the flap during the healing process with the single buccal mucoperiosteal flap.

The dorsal and ventral labial arteries and the angular artery provide vascularization to the buccal mucosa, and preservation of blood supply is important. Long, narrow, skinny flaps may have inadequate blood supply and lead to necrosis of a portion of the flap with subsequent failure. The epithelial margins of the flap are removed with a sharp #15 scalpel blade or La Grange scissors. Following elevation of the mucoperiosteal flap, further “freshen the margins” with a medium diamond bur to ensure removal of all the epithelial tissues and perform an osteoplasty on any irregular, rough bone margins. Fresh vascularized margins will allow first-intention healing to occur following apposition and suturing. The mucoperiosteal flap is elevated using a periosteal elevator directed toward the bone and moving in an apical direction. Care is taken not to perforate the mucosa, which will diminish the success of the procedure. Perforated flaps leave mucoperiosteal defects and suture lines over bone defects and not over underlying bone, resulting in failure of the repair. Closure of the mucoperiosteal flap without tension and harvesting a large, broad-based flap with appropriate releasing incisions are requirements. Additionally, releasing the oral mucosa and connective tissue from the periosteum with a careful scalpel incision or blunt surgical scissor dissection allows the flap to be released and easily moved to cover the defect without tension.

A broad-based mucoperiosteal flap can be created to cover an oral nasal fistula from a maxillary canine tooth by incising from distal aspect of 103/203 (third incisors) to distal 105/205 (1st premolars) (being absolutely certain to return gingiva around 105/205 with the flap closure if the tooth/teeth are present) or equivalent, depending on the presence and absence of adjacent teeth. Larger flaps may need to be created dependent on the size of the bone defect. In some instances, mucoperiosteal flaps to the region of the maxillary 4th premolars (108/208) are necessary. Following release of the flap, removal of epithelialized tissue margins, and osteoplasty of the bone defects, the flaps are initially apposed and sutured at the vertical release corner margins to the palatal mucosa. After the flap is anchored, the fresh margins of the palatal mucosa and free margin of the mucoperiosteal flap are sutured. Finally, the vertical releasing incisions are sutured in opposition. The simple-interrupted sutures are placed approximately 2 mm apart and no less than 2 mm from the incision. Suture choices for surgical flap closure include poliglecaprone-25, polyglactin 910. Polydioxanone is not an appropriate suture for the oral cavity due to its long degradation time and potential to cause foreign body reactions while persisting in the oral cavity.

**Inverted Palatal Mucosal Flap with Buccal Mucoperiosteal Flap (Double-Flap Technique)**

The author rarely ever has to utilize this technique. The palatal flap creates an immediate epithelial surface adjacent to the nasal cavity. A full-thickness palatal flap is created by incising the palatal mucosa parallel to the mesial and distal margins of the defect near or past the midline of the palate. Hemorrhage is anticipated from the vascular palatal mucosa and the major palatine arteries and its terminal branches. The palatal artery may need to be ligated and digital pressure applied to the region
to temporarily control bleeding. The palatal mucosa, adjacent to the defect, acts as a hinge as the palatal flap is inverted to cover the oronasal defect. A second flap as described previously (single buccal mucoperiosteal flap) is created and sutured over the inverted palatal flap. The palatal defect is allowed to heal by second intention. A potential troublesome consequence with this technique is exposure of the nasopalatine foramen. Additional, more complicated palatal surgery would then be necessary to close the defect created by the surgeon. This can be prevented with knowledge of anatomy and using a split-thickness flap, if necessary.

**Postoperative Recommendations**

1. Soft food only for 10–14 days
2. No chews or toys for 10–14 days
3. 0.12% chlorhexidine gluconate rinse every 12 hours for 10–14 days
4. Minimal client handling of the flap and lip
5. Elizabethan collar to prevent patient from rubbing or pawing at the incision as indicated
6. Postoperative antibiotics (clindamycin or amoxicillin/clavulanic acid)
7. Postoperative pain medication (NSAIDs, tramadol, etc., as indicated based on underlying metabolic/systemic disease and concurrent medications)
8. Written discharges to ensure client compliance
9. Recheck in 14 days

**References**

References are available upon request.
Managing Differing Nutritional Needs in the Multi-Cat Household
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Multiple Cats, Multiple Needs
The goal within a multi-cat household is to: 1) determine an appropriate base/common denominator diet available to everyone, achieving a feeding strategy that puts no one at risk nutritionally, as well as 2) to meet any additional individual nutritional needs of each member of the group as closely as possible twice or more times a day “behind closed doors.” This requires analyzing the clowder’s nutritional needs, personalities and physical abilities.

In order to determine what doesn’t put anyone at risk, we need to think about what disease condition is most responsive to or, the reverse, most damaged by feeding the wrong diet. In other words, which cat is most fragile, from a nutritional point of view? Cats are obligate carnivores. This concept is central to understanding the nutritional needs of cats and planning dietary therapies for health disorders, especially when dealing with multiple cats with differing health considerations. We need to review basic nutritional needs of this species before we can decide what modifications can be made safely.

Food, Feeding and Nutrition in a Feline Context
Cats diverged from dogs approximately 30 million years ago, evolving metabolically into obligate carnivores with unique strategies for the utilization of protein and amino acids, fats and vitamins. This concept must be at the centre of trying to understand the nutritional needs of cats and planning dietary therapies for health disorders. Domestic cats have not evolved from the wild cat model. They are anatomically and physiologically adapted to eating as many as 10–20 small meals (a reflection of their hunting behaviour) throughout the day and night. This allows them to hunt and eat when their prey are active. Small rodents make up the majority of their diet, with rabbits, birds, insects, frogs and reptiles making up a smaller proportion. The average mouse provides ~ 8% of an average feral (i.e., active, unaltered) cat’s requirements. Repeated hunting throughout a 24-hour period is needed to meet this need, resulting in the normal grazing behaviour of domestic cats.

Being obligate carnivores has affected everything about cats: their hunting behaviour; that they eat many small meals a day alone; the small size of their stomach; their lack of salivary amylase; their social structure. Cats are hunters, yet the drive to hunt is independent from the need to eat. Hence, feeding more food doesn’t stop them from killing birds or mice - it merely makes them gain weight. Most cats need 10–15 attempts to be successful at killing prey, thus the drive to “eye, stalk, pounce and kill” is permanently turned on to avoid starvation. The average mouse provides 30–35 kcal of energy. Needing 50 kcal/kg ideal weight/day, the 5-kg cat needs 250 kcal or 8 mouse-sized portions/day. These meals are spread out throughout the day, not consumed all at once.

Feeding twice a day or having a bowl that is never empty is not a “natural” way for cats to eat. A 30-kcal meal is approximately 10 pieces of an average maintenance dry food; even eating 10 extra pieces/day results in a 10% (1 lb) weight gain/year. Our need for interaction with our cats also contributes to obesity. Cats generally interact with us frequently and at a low intensity/casually; people generally want fewer, more intense/focused periods of interaction with them. Eating is not a social activity for cats. We may feel like a bad provider or rejected if our cats don’t eat their food eagerly and seek second helpings. And, because their meals are so small, we misunderstand and want them to eat more. We try different diets until we have “evidence “that they enjoy their food. We train them to ask for food and they train us to respond to their boredom or other unmet needs by feeding them.
Opportunities to express hunting behaviour are a basic need for a cat. If a cat doesn’t have the opportunity to hunt, toys meeting appropriate criteria are small (prey-sized), make high-pitched squeaks or cheeps, and move in a rapid, unpredictable fashion. The Indoor Pet Initiative offers an informative piece on choosing the correct toy for an individual cat: http://indoorpet.osu.edu/cats/basicneeds/preypref/index.cfm. Allowing them to hunt for their food (bowl) or using a feeding toy are mentally stimulating activities.

Examples of feeding toys include:
- Multivet Slim Cat (www.petsafe.net/products/feeder-systems/slimcat-interactive-feeder-orange)
- Cat Activity Fun Board (www.traininglines.co.uk/cat-activity-fun-board-interactive-toy.html)
- Go!Cat!Go! Play-N-Treat balls
- FUNkitty Egg-Cersizer (www.premier.com)
- Aikiou Stimulo (http://aikiou.com/stimulo-cat-bowls-and-feeder/)
- Catit Design Senses Feeding Maze (http://ca-en.hagen.com/Cat/Feeding/Accessories/50745)

Cats are very sensitive to the feel of a food (physical form), its odour and taste. They eat their prey head-first. This is a tactile response to the sensation from the direction of the hair/feathers. Most cats prefer foods that are solid and moist, like flesh - not powdery, sticky or greasy. They prefer their food at fresh-killed body temperature rather than room temperature, out of the refrigerator or hot.

Under stressful situations, cats will refuse a novel food; under other circumstances, the same cat may be very adventuresome and choose a new diet over their familiar food. A new diet is more likely to be accepted if it is offered at home rather than in the clinic setting.

Numerous studies have been performed, all showing that spaying and neutering/castration decrease energy expenditure by 7–33%. It is, therefore, very important to counsel clients to change from a growth to an adult formulation and to restrict the caloric intake after surgical altering. In general, unaltered cats need 60–80 kcal/kg/day; after altering, they need about 40–50 kcal/kg ideal body weight/day.

While other species are able to rest their metabolic pathways from the efforts of glucose (energy) synthesis when they have been fed, cats must continue gluconeogenesis in both the fed and fasted states. When anorectic, they catabolize body proteins. Protein supplementation during fasting will slow hepatic lipid accumulation. Urea cycle enzymes in the liver of cats are always “turned on.” Adult cats have a much higher requirement for protein than do dogs or humans. Expressed as a percentage of diet, adult cats need 29% vs. the adult canine requirement of 12% or the human need for 8%. Over the long term, cats can adapt to lower protein diets and use carbohydrates as an alternate energy source. In a paper that is in press (J Feline Med Surg) at time of writing these notes (Feb 2013), Laflamme has shown that healthy cats need a minimum of 5.2 g protein/kg/day in order to maintain a neutral nitrogen balance.

An elegant study (Hewson-Hughes 2011) has shown that when cats are able to choose the constituents of their diet, they will aim for a macronutrient profile of 52% protein, 36% fat and 12% carbohydrate. This fits with the many studies of the diets of free-roaming feral cats. In a review of 27 studies, Plantinga showed that the native diet consists of 52% protein, 46% fat and only 2% carbohydrate.

**Quantity to Feed**
Fifty kcal/kg/day provides a rough guide and refers to ideal body weight. If a cat is overweight, calculate their caloric requirement for maintenance at their ideal weight. This “rule-of-thumb” is adequate for
calculations to determine how much a patient should be getting on a daily basis in clinic and as a starting point for the patient when they are discharged. The client should be advised of the actual amount of food to feed when sent home with canned or dry food. Make sure that you are communicating with common vocabulary, as what one person thinks of as a “cup” may not be an 8-oz/250-ml measuring cup. The most accurate method for measuring food quantities is by using a kitchen scale.

Once feeding any therapeutic diet, it is very important to check and see how the individual patient is responding to the diet by reevaluating them, just as we would recheck a patient on any other medical therapy. Checking body weight and condition cannot be done over the phone. For cats outside of the 2- to 7-kg (5- to 16-lb) range in ideal condition, the 50 kcal/kg/day formula isn’t accurate enough. The following formula is more appropriate: $70 (BW \text{ in } kg)^{0.75}$ (raised to the 0.75 power).

Example: For an 18-lb (8.1 kg) cat:

$8.1 \times 8.1 \times 8.1 = \text{BW cubed} = 534.4$

Hit square root button twice on calculator => 23 then => 4.8

$x \times 70 = 336.$

Using 50 kcal x 8.1 kg = 405 kcal, resulting in overfeeding. Likewise, for a 1-kg kitten, the more accurate formula results in 70 kcal vs. the simpler formula, which would undernourish at 50 kcal/day.

Table 1 provides resting energy requirements (RER) for ideal body weight.

<table>
<thead>
<tr>
<th>Cat</th>
<th>Body condition score 5/9</th>
<th>RER*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Body weight (lbs)</td>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>1</td>
<td>0.45</td>
<td>0.91</td>
</tr>
<tr>
<td>2</td>
<td>1.36</td>
<td>2.27</td>
</tr>
<tr>
<td>3</td>
<td>1.82</td>
<td>2.73</td>
</tr>
<tr>
<td>4</td>
<td>3.18</td>
<td>3.64</td>
</tr>
<tr>
<td>5</td>
<td>3.64</td>
<td>4.09</td>
</tr>
<tr>
<td>6</td>
<td>4.09</td>
<td>4.55</td>
</tr>
<tr>
<td>7</td>
<td>4.55</td>
<td>5.82</td>
</tr>
<tr>
<td>8</td>
<td>5.82</td>
<td>6.82</td>
</tr>
<tr>
<td>9</td>
<td>6.82</td>
<td>9.09</td>
</tr>
<tr>
<td>10</td>
<td>9.09</td>
<td>11.36</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\text{RER} = [\text{BW(kg)}^{0.75} \times 70]$

$\text{Growth DER (Kcal/day): Growing kittens} = 2.5 \times \text{RER}$

$\text{Maintenance DER (Kcal/day):}$

Normal, neutered adult = 1.2 x RER

Intact adult = 1.4 x RER
Obese prone = 1.0 x RER
For weight loss = 0.8 x RER

RER - Resting energy requirement: the energy required for a normal individual at rest in a thermoneutral environment based on body weight.
DER - Daily energy requirement: the average daily energy expenditure of an animal dependent on life stage and activity (work, lactation, gestation, growth).

**FEEDING FOR LIFE STAGE OR USING THERAPEUTIC DIETS AS PART OF DISEASE MANAGEMENT**

Let’s apply this overview of very basic nutrition and feline feeding facts to a multi-cat home with multiple nutritional needs to a household consisting of the following 12 individuals:

1. An elderly cat with International Renal Interest Society (IRIS) stage 3 renal insufficiency
2. A thin, arthritic cat
3. A 4-month-old healthy kitten
4. A 2-year-old healthy cat
5. A 7-year-old obese cat (body condition score [BCS] 8/9, high morphometric measurement)
6. An adult cat with “IBD” who vomits and gets diarrhea readily
7. A 10-year-old cat with diabetes
8. A 7-year-old chronically constipated cat
9. A 9-year-old cat with CaOx history
10. A 2-year-old cat with struvite crystalluria
11. A cat with hepatic lipidosis
12. A 14-year-old hyperthyroid cat

What dietary strategy can accommodate what appear to be completely disparate nutritional needs?

**Feeding Cats with Renal Disease**

We would like to feed the first cat, an elderly individual with stage 3 renal disease, a protein-restricted diet suitable for renal insufficiency. Do all cats with renal disease have the same etiologic cause for their decline in renal function? Are they all at the same stage? Do they have identical nutritional requirements? Could this cat, perhaps, benefit from being fed a protein-enhanced diet, a recuperative diet, a growth diet, a senior diet or a maintenance diet?

**Protein: calorie malnutrition** occurs when a cat is getting enough calories but not enough of them come from protein. As a result, there may or may not be weight loss, but there will be muscle wasting as well as a deterioration in the hair coat quality. Because protein is a component in antibodies, immune function may be compromised; anemia may be exacerbated due to the lack of building components for hemoglobin; albumin levels may decrease, and tissue healing may be affected. Protein is a preferred flavour, so if a cat is already inappetent, restricting protein may result in inadequate intake of all nutrients, and the protein intake may fall below that required for normal function.

As an obligate carnivore, if a cat doesn’t get enough dietary protein to meet metabolic requirements, he must draw on endogenous, stored protein sources to meet those needs. Over months, cats can downregulate their protein needs and switch to use other pathways, but in the short and intermediate term, muscle will be catabolized. The resulting muscle wasting and decreased mass reduces the serum level of creatinine (Cr) measured. This makes it difficult to know how much of a Cr decrease seen in a cat fed a restricted protein diet is from improvement in renal function and how much is because there is less functional muscle producing Cr.
Despite numerous experimental studies and clinical trials having been performed, questions about feeding protein to the cat with renal disease still remain. These include the following five:
1. What is the optimal amount of protein for a cat with renal disease?
2. When should protein restriction be implemented?
3. Does the type of protein make a difference?
4. How much restriction is necessary?
5. Will a cat in > stage 2 benefit if phosphorus is restricted by other means?

Protein levels in “restricted” and “high” protein diets fall within the nutritional guidelines, merely at the low or at the high end of the range. Protein-restricted therapeutic diets are not all the same; there are some marked differences in their composition - not just in protein sources and quantities, but also in the calorie source, in their phosphorus, potassium, and sodium content. Table 2 compares reduced protein and phosphorus foods as of December 2012.

<table>
<thead>
<tr>
<th>Product (listed in order of decreasing protein content - all non-acidifying)</th>
<th>kcals/can or cup</th>
<th>Nutrients of concern (/100 kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Protein</td>
</tr>
<tr>
<td>Science Mature Hairball (dry)</td>
<td>326</td>
<td>8.5</td>
</tr>
<tr>
<td>Hill’s y/d (dry)</td>
<td>519</td>
<td>8.2</td>
</tr>
<tr>
<td>Hill’s y/d (5.5-oz can)</td>
<td>188</td>
<td>8.2</td>
</tr>
<tr>
<td>Hill’s g/d (5.5-oz can)</td>
<td>165</td>
<td>8.2</td>
</tr>
<tr>
<td>Hill’s g/d (dry)</td>
<td>297</td>
<td>7.9</td>
</tr>
<tr>
<td>Purina NF (5.5-oz can)</td>
<td>193</td>
<td>7.7</td>
</tr>
<tr>
<td>Purina NF (dry)</td>
<td>398</td>
<td>7.2</td>
</tr>
<tr>
<td>Iams Renal Plus (dry)</td>
<td>514</td>
<td>7.1</td>
</tr>
<tr>
<td>Hill’s l/d (dry)</td>
<td>505</td>
<td>7.0</td>
</tr>
<tr>
<td>Iams Renal Plus (6-oz can)</td>
<td>199</td>
<td>6.8</td>
</tr>
<tr>
<td>Hill’s l/d (5.5-oz can)</td>
<td>183</td>
<td>6.7</td>
</tr>
<tr>
<td>Hill’s k/d (dry)</td>
<td>492</td>
<td>6.6</td>
</tr>
<tr>
<td>Hill’s k/d chicken (5.5-oz can)</td>
<td>183</td>
<td>6.5</td>
</tr>
<tr>
<td>Royal Canin hepatic (dry)</td>
<td>439</td>
<td>6.3</td>
</tr>
<tr>
<td>Royal Canin Renal LP Modified-P (pork) (dry)</td>
<td>428</td>
<td>6.2</td>
</tr>
<tr>
<td>Royal Canin hypoallergenic hydrolyzed HP (dry)</td>
<td>344</td>
<td>6.0</td>
</tr>
</tbody>
</table>
Dietary protein is not, in and unto itself, toxic to kidneys. Because of inherent progression of chronic renal insufficiency, IRIS staging focuses on factors which, when managed, are known to slow progression. These are: azotemia, metabolic acidosis, hyperphosphatemia, proteinuria and hypertension.

Azotemia, metabolic acidosis and, to some degree, hyperphosphatemia are affected by hydration, thus optimizing hydration through the use of canned diets, adding water to food, encouraging drinking by use of flavoured liquids or a fountain, along with the use of daily subcutaneous fluids are beneficial to the well-being of the patient. The patient should enjoy the diet offered, regardless of what illness he/she has. **It is always more important that they eat, rather than what they eat.** And the amount consumed must be monitored. This requires calculating the caloric requirements for each individual. A reasonable goal is 50 kcal/kg/day. By being made aware of how much food this is equivalent to, they can notify the veterinarian should the cat be eating less than that amount. This helps prevent confusion regarding weight loss associated with progressing disease vs. that associated with inadequate nutrient intake.

Returning to the cat in question, we do not know from the description (stage 3 chronic kidney disease) whether the cat is proteinuric or protein replete, nor what the phosphorus or potassium levels are. A protein-restricted diet (which one?) may be appropriate, but one of the other aforementioned diet types (protein-enhanced, recuperative, growth, senior or maintenance) might be the correct diet for this individual cat. Just because someone has a specific illness does not automatically mean that the diet designed for that condition is the best diet for that individual.

Every time we send home a therapeutic diet, we are performing a feeding trial with one subject in it \( n = 1 \). We have to get the cat back into the clinic and see how he/she is doing on that food. How is his weight? Increased? Decreased? How is his coat? Does he eat with enjoyment or vigour? What are his stools like (moist logs or dry pellets, cow patties or coloured water)? How energetic is he since he has been on this diet? Has there been a change in his PCV and proteins? In this case, have the BUN and Cr, the phosphorus and calcium or USG changed? Is he proteinuric and potentially protein deficient? What about his blood pressure? Have these parameters increased or decreased?

**Feeding for Arthritis**

What are the nutritional requirements for cat #2 who is thin and arthritic? Options include a mobility/joint diet or, for weight gain, a kitten diet, a recuperative diet, or possibly a senior diet. Assuming that the physical examination and diagnostics do not reveal a cause for her weight loss, it is reasonable to try a variety of diets including all of the above in case she has become bored with her food. The addition of omega-3 fatty acids appears to be beneficial, as does supplementation with green-lipped mussel extract and glucosamine/chondroitin sulfate.
Feeding Growing Cats and Elderly Cats
Young cats have growth requirements, which include an increased proportion of animal-based protein and more calcium and phosphorus. The 4-month-old kitten (#3) and the 2-year-old healthy adult (#4) would ideally be fed a kitten diet and a maintenance diet, respectively. Elderly cats over 12 years of age have been shown to have an increased need for protein, relative to adult cats. They also need more calories from fat than during their adult stage. In part this is because of a decreased ability to digest and absorb fat and protein.

Feeding Obese Cats
For the fifth cat, #5, the 7-year-old obese kitty with BCS 8/9 (or 4.5/5), the therapeutic strategies may include a high-fiber diet; a high-protein, low-carbohydrate balanced diet; or a low-fat diet.

Exceeding a cat’s protein needs beyond maintenance requirements helps induce satiety. In a study by Laflamme et al., when cats were fed a diet with 45% of calories from protein, cats lost more fat and less lean mass compared with cats fed a diet with 35% of calories from protein, despite similar total weight loss and rate of weight loss.

Traditional belief holds that it is the amount of calories ingested versus expended that is required for loss of weight and that it doesn’t matter which approach we choose (making this cat very flexible), as long as the caloric intake is reduced, the cat isn’t feeling deprived and pestering the client, and the diet is balanced. Given the benefits of achieving lean body mass by feeding a high-protein diet, a goal of at least 40% protein, dry basis, in a low-fat diet (6% to 10% fat) is a healthy approach to take. Feeding closer to the native, Paleolithic high-protein, lower carbohydrate diet may have hormonal benefits that favour lean; however, at this time, this idea has not yet been proven.

The thermic effect of food (TEF) refers to the energy cost of digesting and absorbing food. TEF is higher when meals are small and frequent, so feeding multiple small meals is preferable to feeding one or two large meals. One way to incorporate this into the diet - and give the cat a little challenge (and exercise) - is to divide the day’s food into six or seven small portions, using feeding balls or placing it on saucers throughout the home as if the cat were on a “treasure hunt.” This feeding strategy makes the cat less likely to gorge and entices him or her to look for more - all of which has a higher TEF cost.

Calculating the quantity of dry and/or canned food to prescribe for weight loss:
1. Determine or approximate the cat’s ideal body weight in kg.
2. Calculate the number of calories needed to maintain that ideal weight (wt in kg x 50 kcal/kg/day).
3. Multiply this number by 60–70% to get the amount of calories to feed for weight loss.

Include the calories in the treats and supplements, people food, and pill pockets that the kitty is being given when you figure out the quantity of food to recommend. As with the protein-restricted diets, the compositions of therapeutic diets designed for weight loss are very different from each other.

Feeding Cats with Intestinal Sensitivity
Our dietary choices for cat #6, the adult with the sensitive gastrointestinal tract and a diagnosis of “IBD” are either a limited antigen, a “hypoallergenic” or a hydrolyzed protein diet. Some cats may tolerate a highly digestible, low-residue intestinal diet.

Feeding Cats with Diabetes
Cat #7 is the 10-year-old diabetic. Feeding strategies include a high-protein, low-carbohydrate diet or a high-fiber diet. However, a diabetic cat can be controlled with insulin as long as the diet and treats fed remain consistent from day to day.
Neither carbohydrates nor dry extruded diets are cause of diabetes or obesity. However, exchanging dietary carbohydrate for protein appears to be useful for weight-loss treatment and management of non-insulin-dependent diabetes in cats.

In a prospective, randomized, double-blinded 10-week study (Hall et al.), 12 cats (7/12 obese) - of whom six were newly diagnosed and six were poorly controlled diabetics - evaluated standard maintenance diet vs. lower carbohydrate, higher protein (LCHP) diets. The cats ate dry or canned based on their preference. All were treated with glargine and assessed at weeks 1, 2, 4, 6, and 10 with fructosamine, BG curve, and clinical signs. One cat from each diet group achieved remission by week 10. All cats improved clinically, increased weight and achieved good glycemic control. Those fed the LCHP had a significantly greater decrease in fructosamine. The conclusion, based on this small study, was that using insulin, “frequent monitoring is key to achieving glycemic control in diabetic cats; potential benefits of dietary modification require further evaluation.” The author summarizes all of the preceding studies and approaches: high fiber & low fat, high insoluble fiber vs. low fiber, LCHP canned, low-carbohydrate diet vs. low-carbohydrate diet plus acarbose, low-carbohydrate & low-fiber diet vs. moderate-carbohydrate & high-fiber diet. None of these approaches appears to make a meaningful difference in the small numbers of cats in each study.

Feeding the Constipated Cat
Constipation is, first and foremost, treated through rehydration. As long as cellular dehydration is present, the need will exist to resorb water from renal and gastrointestinal systems. Addition of fiber to the diet should be avoided until the patient is adequately hydrated. Use of enemas, promotility agents and laxatives prior to addressing this underlying problem is ineffective at best and has the potential for exacerbating the problem. Once that has been accomplished (or simultaneously to rehydration), one can focus on assisting the passage of the feces by mechanical or pharmacologic means.

Soluble fibers are helpful in diarrhea; insoluble fibers are beneficial for constipation. Dietary fiber is a combination of soluble and insoluble fibers. Recently a dry diet enhanced with psyllium has been marketed for the treatment of constipation. Along with rehydration, feeding this diet alleviated obstipation in cats with megacolon, allowing them to cease medication and avoid surgery or euthanasia. Another approach is to reduce fiber, feeding a low-residue diet.

Feeding Cats with Lower Urinary Tract Disease
Ensuring that urine is in a neutral pH and stays diluted enough so that mineral components don’t come out of solution (i.e., urine remains under-saturated) will help reduce the chance of either CaOx or struvite crystals forming.

Feeding for Hepatic Lipidosis
The most important thing is that the cat gets adequate calories without restricting protein. Lipidosis is a disorder of lipoprotein metabolism. Additionally, L-carnitine, S-adenosylmethionine, B vitamins and taurine may be supplemented. If the cat has an esophagostomy tube in place, ensuring nutrition is easy if kitty isn’t eating enough on his/her own.

Feeding for Hyperthyroidism
Use of the extremely low iodine-containing diet in a multi-cat household such as this is inappropriate.

For all cats in the household: Make sure that water, the most important nutrient, is readily accessible. Have lots of water stations around the home. They should be in places other than the “kitchen” as well, so that cats don’t have to compete and because cats like to eat and drink in different places.
**Baseline Diet**
The first of the two goals for feeding a multi-cat household is to achieve a feeding strategy that puts no one at risk nutritionally, having the base/common-ground diet available to everyone. Of these 12 cats, the one at greatest risk if fed the wrong diet is the cat with “IBD.” If the cat with renal disease were in IRIS stage 4, he may well be the most delicate, but just getting adequate calories into a uremic cat becomes the main concern at that point, and placing a feeding tube would allow us to deliver an appropriate diet. We would also have to think about a different strategy for restricting access to other diets if he were feeling well enough to be roaming the house. If he is hyperphosphatemic as well as being in stage 3, using intestinal phosphate binders is a viable and necessary alternative to using a restricted protein diet as the baseline, everyone eats, diet. (He can still get the restricted protein diet twice a day.)

**Supplementing Requirements**
The second goal is to meet the individual nutritional needs of each member of the household as closely as possible twice a day “behind closed doors.” Certainly the “IBD”-safe diet can be left out during the day for all cats to eat. Twice daily all cats other than the cat with gastrointestinal disease can be placed in separate rooms to be supplemented with their different or additional needs. This requires analysis of the clowder’s needs as well as their personalities and physical abilities. The elderly cat who is less able to jump can be prevented from eating the food of an agile youngster if the growth diet is placed high up. An overweight cat can be prevented from getting to any food other than that designed for weight loss (the base diet) by putting a latch on a door, building a creep feeder, or using a “keyed” cat flap (such as one that responds to the cats’ preexisting microchips: www.sureflap.ca) so only the thinner cats can get through the narrower space. Treasure hunts using small quantities of food as well as feeding balls (which some cats won’t want to use) will also help. Figuring out creative strategies to use based on the strengths and weaknesses of the individuals is an intriguing challenge and needs to take the cats’ physical, personality, and nutritional profiles into consideration.

Reducing stress in the multi-cat household must always be a focus. Cats are social but with strict social rules and restrictions to keep distance in order to avoid confrontation. Environmental enrichment is extremely important. Ellis writes eloquently about this: www.sciencedirect.com/science/article/pii/S1098612X09002538

**Key Points**
1. Don’t assume that a diet designed for a particular clinical condition is necessarily the best diet for every cat with that condition.
2. The quantities to be fed, listed in product guidelines, are a starting point. Each cat is different.
3. Monitor the clinical response of the individual patient to the dietary prescription.

**References**

**Obesity, a Burgeoning Problem: Weight Loss for the Overweight Cat**

Margie Scherk, DVM, DABVP (Feline)
catsINK, Vancouver, B.C., Canada

Obesity is the number one nutritional disorder in pets in the western world. Twenty-five percent of cats seen by veterinarians in the USA and Canada are overweight or obese.\(^1\) Cats are no different than the rest of us, in that over-consumption of calories results in storage and is manifested as excessive body fat. In optimal condition, cats should carry 15–20% body fat.

In another study in 1998, Scarlett and Donoghue\(^2\) looked at diet and obesity in cats. Using multivariate statistical analysis controlled for age, they showed that obesity is a risk factor for diabetes mellitus, skin problems, hepatic lipidosis, and lameness. A more general look at the consequences of obesity or a chronic overweight state adds the additional risks in other species as well as the cat: hyperlipidemia, insulin resistance, glucose intolerance, feline lower urinary tract disease, anaesthetic complications, dyspnea, Pickwickian syndrome, exercise intolerance, heat intolerance, impaired immune function, exacerbation of degenerative joint disorders and dermatological conditions.\(^3\,^5\) The longer a cat (or person) is overweight, the greater the chance that one of the negative consequences of obesity will occur.

Interestingly, mixed-breed cats were found to be at higher risk for becoming overweight than purebreds. This might be genetic, but husbandry and awareness of the cat may play a role. Because we confine cats indoors, feed them highly palatable and calorie-dense diets (especially dry food) that they do not have to work for, and leave them alone many hours a day - possibly resulting in boredom - our cats are likely to consume excess calories.

Neutering has been shown to reduce the energy requirements (resting metabolic rate) of cats by 20–25%.\(^6\,^7\) A link has been shown between weight and fat gain following gonadectomy and serum leptin levels.\(^8\) It has also been shown that increased leptin levels may contribute to the decreased insulin sensitivity (resistance) seen in overweight cats.\(^9\) In fact, further work has indicated that insulin resistance and glucose intolerance develop in obese cats and that this occurs at an increased incidence in male cats; interestingly, male cats are at increased risk for developing diabetes mellitus.\(^10\)

It is important, therefore, that we counsel our clients to change to an adult formulation and to watch carefully for weight gain and adjust caloric intake accordingly. Ten extra pieces of an average formulation kibble/day above a cat’s energy needs can result in a weight gain of one pound of body fat in one year! So, the quantity we feed obviously can make a difference to weight, but does the frequency of feeding? And research shows that the frequency of feeding, as well as the quantity fed, makes a significant difference.\(^10\) Given innate feline physiology, feeding cats small meals more often and limiting the number of treats offered are the most appropriate feeding strategies, thereby assisting in weight loss.\(^11\,^12\)

Fed optimally, cats reach their adult weight at about 12–15 months of age. This can be used as a guide to determine a cat’s “ideal” adult weight.

**Assessing Body Composition**

It is easier to prevent weight gain than to help a cat lose weight. The prevalence of feline obesity increases after 2 years of age, plateaus until about 12 years, and then declines thereafter.\(^13\) Fed optimally, cats reach their adult weight and body condition score (BCS) at about 12–15 months of age. This can be used as a guide to determine an individual cat’s “ideal” adult size.

What tools do we have to help prevent the development of obesity? At every veterinary visit, determining not only the patient’s body weight and recording it in their medical record, but also
calculating the percent weight change are invaluable tools for the detection of weight-change patterns. Cats with early chronic illness may be identified using this calculation as well.

\[% \text{ weight change} = \frac{( \text{current weight} - \text{previous weight} )}{\text{previous weight}} \]

Use a body condition scale (BCS) at every visit, categorizing subjectively the body condition as emaciated, thin, ideal, heavy or grossly obese (1–9 or 1–5 scale). This scale evaluates contours and silhouettes. In ideal condition, the bony prominences of the body (i.e., pelvis, ribs) can be readily palpated but not seen or felt above skin surfaces. There should be insufficient intraabdominal fat to obscure or interfere with abdominal palpation. Additionally, assessing muscle condition using a muscle score can also help define whether weight is adequately proportioned to lean vs. to fat.

In questionable cases, radiographs and ultrasound may be used to assess falciform fat deposits, paralumbar and perirenal fat. In research settings, dual-energy X-ray absorptiometry (DEXA) evaluation is used for the most accurate bone density, muscle mass and fat calculations.

**WHAT TO FEED**

Simply feeding less of a normal diet is not recommended. Not only will the patient be unhappy and feel hungry, but nutritional balance will be compromised. A diet should be balanced according to energy content. When a cat eats enough of the diet to meet energy requirements, then their protein, vitamin and mineral needs will be met as well. An energy-limiting diet is one that is so energy-dense that a cat will stop eating once energy needs have been met but before protein and other nutrient needs have been met. Similarly, a bulk-limiting diet will cause the individual to stop eating before energy and other nutrient needs have been met.

An elegant study (Hewson-Hughes)\(^{14}\) has shown that when cats are able to choose the constituents of their diet, they will aim for a macronutrient profile of 52% protein, 36% fat and 12% carbohydrate. This fits with the many studies of the diets of free-roaming feral cats. In a review of 27 studies, Plantinga\(^{15}\) showed that the native diet consists of 52% protein, 46% fat and only 2% carbohydrate. Clearly the diet that cats have evolved to eat is one high in protein and low in carbohydrate. And while neither carbohydrates nor dry extruded diets are cause of diabetes or obesity, exchanging dietary carbohydrate for protein appears to be useful for weight-loss treatment and management of noninsulin-dependent diabetes in cats.\(^{16}\) Even so, energy restriction is still required for achieving weight loss in obese cats when dietary carbohydrate is exchanged for protein.

Exceeding a cat’s protein needs beyond maintenance requirements (5.2 g/kg/day)\(^{17}\) helps induce satiety. When they were fed a diet with 45% of calories from protein, cats lost more fat and less lean mass compared with cats fed a diet with 35% of calories from protein, despite similar total weight loss and rate of weight loss.\(^{18,19}\)

There are a number of approaches to feline weight loss:

4. High protein protects (minimizes loss of) lean mass, stimulates cellular energy metabolism and protein turnover, and may enhance satiety.
5. High moisture can reduce caloric density, which promotes short-term weight loss. It takes a few weeks to a few months for cats to adapt to the lower-caloric density (as fed) in canned foods versus dry foods; however, this only works for some cats.
6. High fiber can reduce caloric density and induce satiety. Some cats will self-restrict calorie intake when fed a dry, high-fiber, low-calorie diet.
7. Low fat will reduce caloric density. High-fat diets are a risk factor for inducing obesity and are
generally not considered optimum for a weight-loss diet. That said, some cats will lose weight on a
high-protein, high-fat, low-carbohydrate diet if the calories are restricted appropriately.

Ultimately, it is the number of calories ingested versus expended that is required for loss of
weight. Given the benefits of achieving lean body mass by feeding a high-protein diet, a goal of at least
40% protein, dry basis, in a low-fat diet (6% to 10% fat) or more protein in a higher-fat diet (12% to 16% fat)
is a healthy approach to take.

When discussing with clients why reduced quantities of normal foods won’t result in successful weight
loss, the following may be considered:

- Normal diets are too high in fat.
- Fat is an easy energy source for manufacturing.
- There is less thermic energy formed in the digestion of fat.
- Digestibility is inversely proportional to the amount fed.
- All nutrients are decreased when you feed less of a balanced diet.

An individual’s energy requirements are composed of several components. The daily energy
requirement (DER) = resting energy requirement
+ exercise energy requirement
+ thermic effect of food (TEF)
+ adaptive thermogenesis (AT)

* Unlike metabolizable energy requirement (MER), DER includes energy required for activity, such as
work, gestation, and growth, as well as energy needed for maintaining normal body temperature.
- Resting energy requirement varies with individuals; this accounts for the apparently higher
manufacturer recommendations vs. a given individual’s food needs.
- TEF is the energy spent on digesting and absorbing food. Increasing the frequency of meals and
decreasing their size results in an increased TEF expenditure.
- AT is the energy used to regulate body temperature.
- DER decreases with increasing age.

A CLINIC WEIGHT-LOSS PROGRAM
In order to be successful with any weight-loss program, three components must be in place: diet,
exercise and recheck visits. Without any of these, the client’s desire for their cat to slim down will fail. A
diet alone can’t do it, as recheck visits monitor progress and provide support needed by most people.
Any exercise will help. We need to reduce the number of calories consumed and increase calorie use
and metabolic rate (exercise). Exercising cats could be seen as an oxymoron; however, some dedicated
clients have even designed agility obstacle courses for their cats. Their commitment is the fuel for the
success of the program.

On the initial extended consultation, a comprehensive physical exam is performed to rule out
concurrent medical problems. Baseline blood work may be advisable, depending on the age and
condition of the kitty. A detailed history is collected in order to become familiar with current feeding
habits and routines. Under Weight-Loss Program is a list of useful questions for this purpose.

Ask the client to keep a 1- to 2-week feeding journal in which everyone in the household who gives
the cat anything ingestible, enters the information. The amount of food as well as exact type (brand)
should be recorded. The client can be asked to make this diary before the appointment and bring it
The diet diary provides the material needed to determine the caloric intake that the kitty has been receiving and gaining weight on. This should be compared to the caloric allowance being recommended.

As a rule of thumb, in order to lose weight, a cat needs 60–70% of the calories required to maintain his/her ideal weight. In other words:

1. Determine/approximate ideal weight
2. Calculate calories needed for ideal weight (wt in kg x kcal/kg/day)
3. Multiply this number by 60–70%

Example: Fluffy weighs 18.6 lb (8.4 kg) with a BCS of 9/9 and is currently being fed 375 kcal day.
The goal is 12 lb (5.4 kg) for a BCS of 5–6/9.
12 lb (5.4 kg) x 50 kcal = 271 kcal
Feed 60% to 70% x 271 kcal = 163 to 190 kcal/day
Weight loss of 6.6 lb (3 kg) will take at least 12 months.

Discuss with the client the benefits of weight loss as well as the risks of chronic obesity. Acknowledge them for their concern and praise them for their desire to take action. Be supportive! They are the ones who will have to do the work.

Inform them of the current weight as well as the goal weight. (The goal weight may be higher than the “ideal” weight; the goal is a healthy weight, not a runway model.) Discuss with them the length of time this may take. A safe rate of weight loss is 1/4–1/2 lb/month (0.1–0.25 kg/month). This will help them stay on track. A weight loss of 10% to 15% is realistic and attainable and will provide health benefits.

The thermic effect of food (TEF) is the energy cost of digesting and absorbing food. As mentioned above, the TEF is higher when small, frequent meals are fed, so feeding multiple small meals is preferable to feeding one or two large meals. One way to incorporate this, as well as give the kitty a little challenge (and exercise), is to divide the day’s food amount on to 6 or 7 small saucers and place them throughout the home as if it were a “treasure hunt.” This means that kitty is less likely to gorge, has to look for more, and has a higher TEF cost.

Discuss with the client why cats become overweight. The first thing to recognize is that pet food manufacturers have to make diets extremely palatable, because that is how a consumer judges how much their companion likes it and decides whether to buy it again or not. This means that most cat foods are very energy-dense from fat, as fat is palatable for cats. In addition, because it is convenient to feed ad libitum, cats snack all day on high-calorie kibble and easily eat more than they need. Cats generally lack exercise when compared to the hunter that they are designed as. In the wild, they have to catch 10–20 small meals a day to survive! And, as already mentioned, an indoor environment is not very stimulating; cats may eat out of boredom. Former strays may also have the fear-driven instinct to gorge in case there isn’t another meal.

We may not be what we eat, but what we eat certainly shapes our biology and how we live! Being obligate carnivores has affected everything about cats, from their hunting behaviour to their solitary eating of many small meals a day to the size of their stomach and their lack of salivary amylase to their social structure. Cats naturally hunt for their food, yet the drive to hunt is independent from the need to eat. Hence, feeding more food doesn’t stop them from killing birds or mice; it merely makes them gain weight. On average, a cat needs 10–15 attempts before he is successful at killing prey; thus, the drive to “eye, stalk, pounce and kill” is permanently turned on, else a cat would starve. Given that the average mouse provides about 30–35 kcal or energy, and a cat needs 50 kcal/kg ideal weight/day, the 5-kg cat
needs 250 kcal or 8 mouse-sized portions/day. These meals are spread out throughout the day - not all at one time. Both feeding twice a day or leaving a bowl that is never empty are “unnatural” ways for cats to eat.

Given that a 30-kcal meal is approximately 10 pieces of an average maintenance dry food, even eating 10 extra pieces/day results in a 10% (1 lb) weight gain/year. We also contribute to obesity by our need for interaction with our cats. Cats (in general) interact with us frequently and (as mentioned) at a low intensity/casually. We, on the other hand, generally want fewer, more intense/focused periods of interaction with them. We also feel rejected or like a bad provider if our cats don’t eat their food eagerly and seek second helpings. Eating is not a social activity for cats. And, because their meals are so small, we misunderstand and want them to eat more. We try more and more diets until we have “evidence” that they enjoy their food. And so we train them to ask for food, and they train us to respond to their boredom or other unmet needs by feeding them.

Opportunities to express hunting behaviour are a basic need for a cat. If a cat doesn’t have the opportunity to hunt, toys that meet appropriate criteria are small (prey-sized), make high-pitched squeaks or cheeps, and move in a rapid, unpredictable fashion. The Indoor Pet Initiative offers an informative piece on choosing the correct toy for an individual cat: http://indoorpet.osu.edu/cats/basicneeds/preypref/index.cfm. Also, allowing them to hunt for their food (bowl) or use a feeding toy is mentally stimulating.

Examples of toys of this sort include:
- Multivet Slim Cat (www.petsafe.net/products/feeding-systems/slimcat-interactive-feeder-orange)
- Cat Activity Fun Board (www.traininglines.co.uk/cat-activity-fun-board-interactive-toy.html)
- Go!Cat!Go! Play-N-Treat balls
- FUNkitty Egg-Cersizer (www.premier.com)
- Aikiou Stimulo (http://aikiou.com/stimulo-cat-bowls-and-feeders/)
- Catit Design Senses Feeding Maze (http://ca-en.hagen.com/Cat/Feeding/Accessories/50745)

But, there is more to obesity than energy in and energy expended. A more holistic approach can provide a greater chance of success. We must also consider why the cat is eating more. Is he bored? Is he not receiving enjoyable stimuli from other, healthier sources and is therefore eating? What other aspects of normal behaviour are not available for him to participate in? How is he meeting his “hedonic budget”? Chronic stress (that may be present in the indoor confined cat) results in neuroendocrine changes that predispose to obesity.²⁰

What drives the client? In a very interesting study, Kienzle and Bergler²¹ found that the “positive strokes” received and the behaviours of clients toward their cats differ with the cat’s weight. To quote from the paper itself: “Thirty percent of owners of overweight cats compared with 12% of owners of normal cats stated that they did not feel very happy prior to acquiring a cat, and the cat was intended to console and encourage them. These results are suggestive of 1) a closer relationship between overweight cats and their owners than between normal cats and their owners; 2) more over-humanization of overweight cats than of normal cats; 3) a potential role of overweight cats as a substitute for human companions.” People with overweight/obese cats tend to underestimate their cat’s BCS, talk about different things to their cats than do people living with cats of normal weight. Not surprisingly, people with overweight cats were more likely to get positive feelings from watching their cats eat, whereas people with cats of normal weight spent more time playing with their cats. While there was “no significant difference between the number of meals and snacks and the type of food received by normal and overweight cats. The overweight cats more often received fresh meat and
kitchen scraps or various extra treats added to their regular food,” and cats of normal weight were more likely to get moist food than obese cats.

Somewhat curiously, people with overweight cats were more interested in their own health than clients with cats of normal weight, and, in the reverse, the former considered preventive care for their cat as less important than the latter group of clients.

So, in a cat’s weight, there is an element of meeting the hedonic budget for the person living with the cat. Hence, it is essential that we address the behaviour of the people living with and feeding the cat! Encouraging alternative “strokes,” things that make the person feel good about their interactions with the cat - such as play and feeling proud of achieving weight loss goals - are not to be taken lightly. Positive feedback from us, the veterinary team (the outside environment), as well as self-generated by the client, are key elements to the success of a weight-loss program.

The behaviour modification required to make a weight-loss program successful needs all key family members to play a role. Are there other forms of interaction that the client can have with the kitty, other than feeding? Treats are the downfall of many a weight-control program. It is best if one person handles all of the feeding and others bond through other means (catnip, combing, playing). As mentioned earlier, feeding multiple small meals as a treasure hunt is beneficial. Developing a routine of playing with a “cat dancer” (a handheld flexible wire with a toy on the end) several times a day will add interest and exercise to the kitty’s life. The cost of the program might include a bag of catnip and a cat dancer (toy).

Create a bar graph to maintain in the clinic computer and kitty’s medical record. Update and send the updated graph home with the client at every visit as a good reminder of their success.

![Weight Loss Graph]

Weight-Loss Program
- Initial 40-minute consultation with DVM: comprehensive physical examination to rule out medical problems
- Evaluate feeding diary (minimum 1-week feeding diary)
- Evaluate current feeding habits and routines
- During the initial weight-loss consultation, it is important to ask questions such as these:
  - What specific amounts and types of food (all, including treats) are fed to the cat? Does the cat drink milk? Is he or she fed “people” food?
10. Who feeds the cat’s regular meals? Do family members routinely feed treats and table scraps?
   - How often is the cat fed? Is the food measured?
   - Does the cat nibble or gorge?
   - Where is the cat fed?
   - Does the cat receive any medications? If so, are the medications given in food or with a treat?
   - Is the cat indoor or outdoor? If outdoor, does he or she routinely hunt?
   - What other pets are in the household?
   - Do other pets have access to the overweight cat’s food?
   - Does the overweight cat have access to the other pets’ food?
   - What is the activity level of the cat?
   - Are there any known stress factors in the home environment?

- Calculate current caloric intake
- Calculate recommended caloric intake: 60–70% of intake required for goal body weight (may need to use 50% if very inactive)
- Send home a “weight loss pack” with food samples (dry and canned) for kitty to choose from.
- Discuss:
  - Realistic goals
  - Risks of obesity
  - Why cats become overweight
  - Behaviour modification

- Follow-up is the key to the success of any weight-loss program! A technician or nurse (program supervisor) should become the client’s “buddy” and be in charge of the follow-up. No weight-loss program is effective without follow-up!
  - Week 1: Support phone call
  - Week 2: 15-minute visit with program supervisor and veterinarian
    - Weigh-in (same scale)
    - Conversation about highlights, problems
    - Update graph
  - Every 2 weeks come in for weigh-in
    - Update and send home graph
  - After 4 months, a 15-minute visit with the supervisor is advisable, because a plateau may occur, and new calculations may be needed to promote further safe weight loss.

Included in the program cost is unlimited buddy phone support. The program lasts 6 months and is renewable if necessary.

REFERENCES
Obstetrical Emergencies
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The periparturient period can be associated with high morbidity and even mortality for the dam and neonates. The periparturient period is defined here as the immediate prepartum period (1–2 weeks before parturition) and the 30- to 45-day postpartum period before weaning. The diagnosis of periparturient problems first requires their recognition and differentiation from normal situations; effective treatment depends on both a timely diagnosis and therapeutic intervention.

Premature Labor
Late-term gestational loss attributed to preterm or premature labor is a controversial topic in small animal reproduction. Both hypoluteoidism and inappropriate uterine activity accompanied by cervical changes have been implicated in the pathophysiology of preterm birth in veterinary medicine, but the syndrome is not well understood or even researched. While the human literature is abundant on the topic, publications on the topic are few in veterinary medicine.

Premature labor is defined here as uterine activity and cervical changes leading to the loss of pregnancy via resorption or abortion before term, for which no metabolic, infectious, congenital, traumatic or toxic cause is identified. Premature labor is associated with progesterone levels that are < 2 ng/ml. Premature labor is often a retrospective diagnosis, achieved after thorough evaluation of the dam and fetuses has been performed because of loss of pregnancy. This evaluation should include metabolic screening of the dam for systemic disease, infectious disease evaluation, histopathology of expelled fetuses and placentae, and review of kennel/cattery husbandry including nutrition, medications and environmental factors. All results are normal or negative. Dams experiencing premature myometrial activity in one pregnancy may or may not exhibit it during subsequent pregnancies, but the syndrome can be a chronic cause of failure to reproduce.

In human medicine, preterm birth complicates 10–12% of human pregnancies, but it accounts for 80% of fetal morbidity and mortality. The diagnosis of preterm labor placing the fetus at risk of premature delivery is dependent upon evaluation of uterine contractility by tocodynamometry, and fetal fibronectin and transvaginal cervical length measurement determined via ultrasonography, which together have high negative predictive value. Amniocentesis is also advocated as a method of evaluating fetal lung maturation and microbial invasion of the amniotic cavity. The presence of contractions alone does not warrant intervention. Tocodynamometry identifies labor onset earlier than subjective maternal perceptions, and home uterine monitoring is advocated in high-risk groups as an initial screening test. Multifetal gestations (i.e., litters) are associated with exaggerated physiologic changes which promote premature labor and complicate tocolytic therapy. Women with histories of preterm deliveries do appear to be at risk for such in subsequent pregnancies.

If intervention is indicated, tocolytics agents have been commonly advocated. Antibiotics, bed and pelvic rest and hydration do not appear to have benefit. Contraindications to tocolytics therapy include severe preeclampsia, placental abruption, intrauterine infection, lethal congenital or chromosomal abnormalities, advanced cervical dilatation, and evidence of fetal compromise or placental insufficiency. Tocolytic agents inhibit myometrial contractions and include beta mimetics (terbutaline, ritodrine), magnesium sulfate, calcium channel blockers and prostaglandin synthetase inhibitors (indomethacin, ketorolac, sulindac). Contraindications to beta mimetics include maternal cardiac arrhythmias, poorly controlled diabetes mellitus and hyperthyroidism; fetal and maternal tachycardia and myocardial ischemia, maternal pulmonary edema and hypotension and fetal myocardial hypertrophy, hyperglycemia and hyperinsulinemia are potential side effects. A contraindication to magnesium sulfate
is maternal myasthenia gravis; side effects include maternal lethargy, muscle weakness, headache, pulmonary edema and cardiac arrest, and fetal respiratory depression, hypotonia, lethargy and demineralization. Contraindications to calcium channel blockers include maternal cardiac disease, renal disease and hypotension; side effects include maternal nausea, hypotension and headache. Contraindications to prostaglandin synthetase inhibitors include maternal renal or hepatic impairment; side effects include maternal nausea and gastroesophageal reflux disease, and fetal constriction of the ductus arteriosus, pulmonary hypertension, reversible renal impairment, intraventricular hemorrhage, hyperbilirubinemia and necrotizing enterocolitis. Physicians hope to intervene in the future with anticytokine (interleukin-10) and antiprostaglandin therapy to more completely suppress the pathogenic process at multiple sites along the pathway rather than just treating the processes at the end of preterm labor.

Small human trials based on prophylactic treatment with progesterational compounds have been reported. Not all reported positive results with meta-analysis, the prevention of preterm delivery or the prevention of recurrent miscarriage appear to be based on the use of only the natural metabolite of progesterone, 17 alpha-hydroxyprogesterone caproate (17P). In one study, no increase in the rate of congenital anomalies in the progesterone group was noted over the control group. The benefit of 17P in preventing preterm delivery appears to be best in a cohort of women at very high risk, and the cohort still exhibited a high rate of preterm delivery (36%) despite significant reduction as compared to untreated control (54%), indicating that other causes of preterm delivery were at play. Tocolytic therapy was added in 17% of the treated group and 16% of the untreated control group. Interestingly, serum progesterone levels were not reported.

The maintenance of canine and feline pregnancy requires serum progesterone levels of > 1–2 ng/mL. Serum progesterone levels during pregnancy normally range from 15 to 90 ng/mL, declining gradually during the latter half of gestation and falling abruptly at term (usually the day before or the day of parturition). Progesterone promotes the development of endometrial glandular tissue, inhibits myometrial contractility (causes relaxation of myometrial smooth muscle), blocks the action of oxytocin, inhibits the formation of gap junctions, and inhibits leukocyte function in the uterus. In several species, local changes in the progesterone level or the ratio of progesterone to estrogen in the placenta, decidua or fetal membranes is important in the initiation of labor. Progesterone antagonists administered at term can result in an increased rate of spontaneous abortion. In the bitch, the corpora lutea are the sole source of progesterone, while in the queen, placental progesterone production occurs in the latter half of gestation. Canine luteal function is autonomous early in pregnancy but supported by luteotrophic hormones (LH and prolactin) after the second week of gestation.

Hypoluteoidism, primary luteal failure occurring before term gestation, is a potential but not yet documented cause of late-term abortion in otherwise normal bitches. It has been documented that the induction of abortion in a normal but undesired pregnancy requires a reduction of plasma progesterone levels < 2 ng/ml. The diagnosis of gestational loss caused by premature luteolysis is difficult, requiring documentation of inadequate plasma progesterone levels prior to abortion for which no other cause is found. Measurement of precise progesterone levels, especially in the critical 1–3 ng/ml range, is not accurate using currently available rapid in-house ELISA kits, necessitating the use of commercial laboratories in most practice situations. A few academic and human private laboratories provide more rapid (< 8 h) turnaround, facilitating the diagnosis.

Progesterone levels diminish in response to fetal death, thus documentation of a low progesterone level after an abortion does not establish the diagnosis of hypoluteoidism as the primary cause for reproductive failure. Administration of progesterone to maintain pregnancy in dams with primary fetal abnormalities, placentitis, or intrauterine infection can cause continued fetal growth with the possibility of dystocia and sepsis. Administration of excessive progesterone to maintain pregnancy in a dam not
actually requiring therapy can delay parturition and impact lactation, endangering the life of the bitch and her fetuses, and it can masculinize female fetuses.

Dams with documented low progesterone levels and historical late-term loss of pregnancy with no apparent pathology can also be evaluated for premature myometrial activity mid gestation, using uterine monitoring. Elaboration of prostaglandins from the endometrium and placenta associated with premature myometrial activity can result secondarily in luteolysis. Premature uterine activity endangering fetal survival can be identified before significant luteolysis occurs, and intervention indicated if the pregnancy is normal otherwise. Pharmacologic intervention to decrease myometrial activity is indicated, using progestational compounds and tocolytic agents alone or in combination.

Therapeutic intervention in primary hypoluteoidism can be accomplished with the administration of injectable natural progesterone or oral synthetic progestogens. Total serum levels of progesterone can be monitored only when supplemented with the natural product. Progesterone in oil is given intramuscularly at 2 mg/kg q 72 h. Altrenogest (Regu-Mate, Hoechst-Roussel), a synthetic progestogen manufactured for use in the mare, is dosed orally at 0.088 mg/kg q 24 h. Both forms of supplementation must be discontinued in a timely fashion so as not to interfere with normal parturition, within 24 h of the due date with the oral synthetic product, and within 72 h with the natural, injectable depot form. This requires accurate identification of gestational length via prior ovulation timing (parturition expected to occur 64–66 days from the LH surge or initial rise in progesterone, or 56–58 days from the first day of cytologic diestrus). Less accurate identification of gestational length can be made from breeding dates (58–72 days from the first breeding), radiography, or ultrasound.

Terbutaline (Brethine, Ciba Geigy) 0.03 mg/kg PO q 8 h has been used to suppress uterine contractility in bitches and queens with historical loss of otherwise normal pregnancies preterm. The dose is ideally titrated to effect using tocodynamometry. Therapy is discontinued 24 h before term.

Further work evaluating the pathophysiology of premature labor and preterm delivery in the bitch and queen is needed, including evaluation of the ovary, placenta, myometrium and fetus for contributing factors. Multicenter studies including identification of the criteria for diagnosis of significant premature labor, specific therapy, outcome and followup (dam and neonatal health, subsequent pregnancies) is encouraged.

**METABOLIC CONDITIONS**

Gestational diabetes occurs infrequently in the bitch and queen and is attributed to the anti-insulin effect of progesterone (mediated by increased levels of growth hormone) during the luteal phase. Polydipsia, polyuria and polyphagia with weight loss occur. Higher protein, lower carbohydrate diets may be helpful in the queen, while high-fiber diets promote euglycemia in the bitch. Insulin may be indicated. Oversized fetuses can result from their increased production of insulin in response to maternal hyperglycemia, and may cause dystocia due to fetal-maternal mismatch.

Pregnancy toxemia in the bitch occurs as a result of altered carbohydrate metabolism in late gestation resulting in ketonuria without glycosuria or hyperglycemia. The most common cause is poor nutrition or anorexia during the last half of gestation. Hepatic lipidosis can occur. An improved plane of nutrition can resolve the condition in most cases, but termination of the pregnancy may be indicated in severe cases.

Puerperal tetany or eclampsia occurs most commonly during the first 4 weeks postpartum, but can occur in the last few weeks of gestation. The condition occurs in bitches more frequently than queens. Puerperal tetany can be life-threatening, caused by a depletion of ionized calcium in the extracellular compartment. Predisposing factors include improper perinatal nutrition, inappropriate calcium supplementation and heavy lactational demands. Small dams with large litters are at increased risk. Excessive prenatal calcium supplementation can lead to the development of puerperal tetany by
promoting parathyroid gland atrophy and inhibiting parathyroid hormone release, thus interfering with the normal physiologic mechanisms to mobilize adequate calcium stores and utilize dietary calcium sources. Thyrocalcitonin secretion is stimulated. The use of a balanced growth (puppy/kitten) formula commercial feed without additional vitamin or mineral supplementation is optimal during the second half of gestation and throughout lactation. Supplementation with cottage cheese should also be avoided, as it disrupts normal calcium-phosphorus-magnesium balance in the diet.

Metabolic conditions favoring protein binding of serum calcium can promote or exacerbate hypocalcemia, such as alkalosis resulting from prolonged hyperpnea during labor or dystocia. Hypoglycemia and hyperthermia can occur concurrently. Therapeutic intervention should be initiated immediately upon recognition of the clinical signs of tetany, without waiting for biochemical confirmation. The signs preceding the development of tonic-clonic muscle contractions (progressing to seizures) include behavioral changes, salivation, facial pruritus, stiffness/limb pain, ataxia, hyperthermia and tachycardia. Immediate therapeutic intervention should be instituted with a slow intravenous infusion of 10% calcium gluconate (1–20 ml) given to effect. Cardiac monitoring for bradycardia and arrhythmias should accompany administration; their occurrence warrants temporary discontinuation of the infusion and a slower subsequent rate. Because cerebral edema can occur from uncontrolled seizures, diazepam (1–5 mg intravenously) or barbiturates can be used to control persistent seizures once eucalcemia is attained. Mannitol may be indicated for cerebral inflammation and swelling. Corticosteroids are undesirable, because they promote calciuria, decrease intestinal calcium absorption and impair osteoclasia. Hypoglycemia should be corrected if present, and exogenous treatment for hyperthermia given if necessary. Once the immediate neurologic signs are controlled, a subcutaneous infusion of an equal volume of calcium gluconate - diluted 50% with saline - is given, repeated q 6–8 h until the dam is stable and able to take oral supplementation. Calcium gluconate or carbonate (10–30 mg/kg q 8 h) should be instituted. Each 500-mg calcium carbonate tablet (TUMS) supplies 200 mg calcium. Efforts to diminish lactational demands on the dam and improve her plane of nutrition are indicated. If response to therapy has been prompt, nursing can be gradually re instituted until the neonates can be safely weaned, usually at a slightly early age (3 weeks), and concurrent supplementation with commercial bitch/queen milk replacement is encouraged. The administration of calcium throughout lactation, but not gestation, may be attempted in dams with a history of recurrent eclampsia (calcium carbonate 500–4000 mg/dam/day divided).

**Infectious Disease**

**Canine Herpesvirus**

Adequate exposure of a nonimmune bitch to canine herpesvirus (CHV) during the last three weeks of gestation can result in infection of the dam and subsequently her neonates. Venereal transmission is believed to be rare and community (respiratory) transmission more common. Signs in the bitch are usually limited to a mild, clear upper respiratory discharge and soft sneezing. Late-term abortion or neonatal death within the first few weeks of life commonly results. The recently infected bitch generally has minimal clinical signs, but has inadequate time to form protective maternal antibodies and allow passive immunity (transplacental or transmammary) to be acquired by the neonates. Incompletely developed immune systems and inadequate thermoregulation during the first days of life make neonates vulnerable to systemic infection (bacterial and viral). Adequate ingestion of colostrum must occur promptly postpartum for puppies to acquire passive immunity. The transmission of protective immunity (placental or colostral antibodies) between a bitch and her puppies depends upon the prior existence of adequate serum maternal antibodies.
Transmission of CHV from an infected, viremic dam to neonates occurs subsequent to contact with infectious vaginal fluids or oronasal secretions. Signs in the neonate are progressive and severe and include anorexia (poor weight gain), dyspnea, abdominal pain, incoordination, diarrhea, serous to hemorrhagic nasal discharge and petechiation of the mucous membranes. The mortality rate in untreated litters infected in utero or during birth is commonly 100%, with deaths occurring during the first few days to 3 weeks of life. Infection in neonates born to a nonimmune bitch may also result from contact with CHV from another dog shedding the organism in the vicinity. Older naive (> 3–4 weeks of age) puppies exposed to herpes virus may have an inapparent infection, but later central nervous signs including blindness and deafness have been observed. Subsequent litters of the bitch infected during a pregnancy are usually resistant to infection, having acquired circulating maternal antibodies.

Canine herpesvirus is a commonly blamed cause for fading puppy syndrome resulting in neonatal death. Premortem diagnosis of CHV infection in neonates can be challenging. Postmortem diagnostics include appropriate histopathology and virus isolation. Pathognomonic changes occurring in the kidneys include multifocal petechial hemorrhages, although this can be seen with bacterial septicemia and associated thromboembolic disorders as well. Intranuclear inclusion bodies can be difficult to find. Diagnosis by virus isolation or CHV-specific PCR is confirmatory and desirable, especially before litter mortality reaches 100%.

Until recently, treatment of CHV infection in neonates has been reported to be unrewarding and rare, with recovery suspected to be associated with residual cardiac and neurologic damage. Treatment with immune serum from affected dams is reported to be ineffective in infected puppies. Vaccine development is hampered by the poor immunogenicity of the herpes virus, as evidenced by other herpesviral vaccines developed for different species, such as feline and bovine rhinotracheitis. Successful treatment with the antiviral agent acyclovir has recently been reported.

Acyclovir is an antiviral agent with activity against a variety of viruses including herpes simplex. Acyclovir is preferentially taken up by susceptible viruses and converted into the active triphosphate form, inhibiting viral DNA replication. Acyclovir is poorly absorbed after oral administration and is primarily hepatically metabolized. Acyclovir can increase the toxicity of nephrotoxic drugs. The half-life in humans is approximately 3 hours. Its use in veterinary medicine is not well established, and it should be used with caution and only in situations where indicated. The safety and effectiveness in humans < 2 weeks of age is not established. The dose was extrapolated from that for humans (20 mg/kg PO q 6 h x 7 days).

Canine Brucellosis
Brucellosis is the primary contagious infectious venereal disease of concern in canine reproduction. Canine brucellosis is caused by *B. canis*, a small, Gram-negative, non-spore-forming aerobic coccobacilli. *B. canis* was first isolated by Leland Carmichael in 1966. *Brucella abortus*, *B. melitensis* and *B. suis* have occasionally caused canine infections but are comparatively rare. Transmission occurs through direct exposure to bodily fluids containing an infectious dose of organism (semen, lochia, aborted fetuses/placentas, milk and urine). There are $2 \times 10^6$ colony-forming units in an infective dose. Transmission is therefore primarily oral, nasal, conjunctival and secondarily venereal (i.e., through the mucous membranes), the former associated with the ingestion or aerosolization of infectious materials. The aerosol route is especially important if kennel conditions are crowded. Transplacental transmission and direct cutaneous inoculation can occur.

Canine brucellosis has high morbidity but low mortality in the adult dog. The clinical systemic signs are often subtle (suboptimal athletic performance, lumbar pain, lameness, weight loss, lethargy). The primary clinical sign of canine brucellosis in the breeding bitch is pregnancy loss, which can occur early (day 20) in gestation, resulting in fetal resorption, or more commonly (75%) later in gestation (generally
45–59 days), resulting in abortion. Bitches with pregnancy loss early in gestation can appear to be infertile (failed to conceive) unless early ultrasonographic pregnancy evaluation is performed. Nongravid bitches can be asymptomatic or can show regional lymphadenopathy (pharyngeal if orally acquired, inguinal and pelvic if venereally acquired).

Infected dogs and bitches should be removed from breeding programs and quarantined. Eradication of the disease in kennel situations has not been successful without removal (culling) of all infected (current or historically) dogs. Because of the zoonotic potential of the disease and difficulty in actually eradicating the infection, euthanasia of affected dogs has been advised. Infection in household or small hobby kennel dogs often results in client requests for alternatives to euthanasia. Neutering decreases the amount of organism shed in semen and uterine discharge but does not eradicate the infection. Urine shedding can persist, and the organism can be found in internal organs and the bloodstream.

Antibiotic therapy has not been historically rewarding, likely due to the fact that the organism is intracellular and bacteremia periodic. Antibiotic therapy may reduce antibody titers without clearing the infection. Relapses are common. Combination therapy with tetracyclines (doxycycline or minocycline 25 mg/kg BID PO for 4 weeks) and dihydrostreptomycin (10–20 mg/kg BID IM or SC for 2 weeks, weeks 1 and 4) or an aminoglycoside (gentamicin 2.5 mg/kg BID IM or SC for 2 weeks, weeks 1 and 4) has been advocated as being the most successful, but unavailability, nephrotoxicity, parenteral therapy requirements, and expense remain problematic. Recently one study reported a slightly encouraging outcome of therapy with enrofloxacin (5.0 mg/kg BID PO for 4 weeks, often for multiple courses) in a small group of infected dogs and bitches. Enrofloxacin was not completely efficacious in eliminating B. canis, but it maintained fertility and avoided the recurrence of abortions, transmission of the disease to subsequently whelped puppies, and dissemination of microorganisms during parturition. Ultimately, however, most treated individuals remained culture positive.

Private breeders should require screening testing of all bitches presented for breeding and confirmatory negative testing if positive results occur during screening before accepting a bitch into their kennel. Stud dogs should be screened appropriately at least annually. Because of the potential for nonvenereal transmission, screening of maiden dogs and bitches before breeding is also recommended.

**Dystocia**

Although many bitches and queens deliver in the home or kennel/cattery setting without difficulty, requests for veterinary obstetrical assistance are becoming more common. The increased financial and emotional value of stud dogs, brood bitches, toms, queens and their offspring to the pet fancy makes the preventable loss of even one neonate undesirable. Breeding colonies in academic, scientific and industrial facilities need to maximize neonatal survival for financial and ethical reasons. Veterinary involvement in canine and feline obstetrics has several goals: to increase live births (minimizing stillbirths resulting from the difficulties in the birth process); to minimize morbidity and mortality in the dam; and to promote increased survival of neonates during the first week of life. Neonatal survival is directly related to the quality of labor. Optimal management of whelping/queening requires an understanding of normal labor and delivery in the bitch and queen, as well as the clinical ability to detect abnormalities in the birthing process.

Dystocia is defined as difficulty in the normal vaginal delivery of a neonate from the uterus. Dystocia must be diagnosed in a timely fashion for medical or surgical intervention to improve outcome. Additionally, the etiology of dystocia must be identified for the best therapeutic decisions to be made.
NORMAL PARTURITION

Gestation
Clinicians are commonly asked to ascertain if a bitch or queen is at term pregnancy, ready chronologically to deliver a litter, and then to intervene if labor has not begun. An accurate determination of gestational length can be difficult, especially if numerous copulations occurred and no ovulation timing was performed. Prolonged gestation is a form of dystocia. Gestation in the bitch is more challenging to calculate than in the cat, because bitches are spontaneous ovulators. Normal gestation in the bitch is 56 to 58 days from the first day of diestrous (detected by serial vaginal cytologies, defined as the first day that cytology returns to < 50% cornified/superficial cells), 64 to 66 days from the initial rise in progesterone from baseline (generally > 2 ng/ml), or 58 to 72 days from the first instance that the bitch permitted breeding. Predicting gestational length without prior ovulation timing is difficult because of the disparity between estrual behavior and the actual time of conception in the bitch, and the length of time semen can remain viable in the bitch reproductive tract (often up to > 7 days). Breeding dates and conception dates do not correlate closely enough to permit very accurate prediction of whelping dates. Additionally, clinical signs of term pregnancy are not specific: radiographic appearance of fetal skeletal mineralization varies at term; fetal size varies with breed and litter size; and the characteristic drop in body temperature (typically less than 99 degrees Fahrenheit) may not be detected in all bitches and varies in many. Breed, parity and litter size can also influence gestational length. Because the queen is an induced ovulator (ovulation follows coitus by 24–36 hours), gestational length can be predicted more accurately from breeding dates, assuming copulation provided adequate coital stimulation for the LH surge and subsequent ovulation, and a limited number of copulations were permitted. The gestational length of queens ranges from 52–74 days from the first to last breeding. The mean gestational length is 65–66 days. Because of the poor outcome with the delivery of premature puppies and kittens, elective intervention is best delayed until stage I labor has begun or prolonged gestation confirmed.

Labor and Delivery
Bitches typically enter stage I labor within 24 hours of a decline in serum progesterone to below 2–5 ng/mL, which occurs in conjunction with elevated circulating prostaglandins and is commonly associated with a transient drop in body temperature, usually to < 100 degrees Fahrenheit (33.7°C). Queens typically enter stage I labor 24 hours after serum progesterone levels fall to less than 2 ng/mL. Monitoring serial progesterone levels for impending labor is problematic due to the fact that in-house canine kits enabling rapid results are inherently less accurate between 2–5 ng/mL, and a rapid decline in progesterone levels can occur over a period of a few hours. Commercial laboratories offering quantitative progesterone by chemiluminescence typically have a 12- to 24-hour turnaround time, which is not rapid enough to enable decisions about an immediate indication for obstetrical intervention.

Stage I labor in the bitch normally lasts from 12 to 24 hours, during which time the uterus has myometrial contractions of increasing frequency and strength, associated with cervical dilatation. No abdominal effort (visible external contractions) is evident during stage I labor. Bitches may exhibit changes in disposition and behavior during stage I labor, becoming reclusive, restless, and nesting intermittently, often refusing to eat and sometimes vomiting. Panting and trembling may occur. Vaginal discharge is clear and watery.

Normal stage II labor in the bitch is defined to begin when external abdominal efforts can be seen, accompanying myometrial contractions to culminate in the delivery of a neonate. Presentation of the fetus at the cervix triggers the Ferguson reflex, promoting the release of endogenous oxytocin from the hypothalamus. Typically, these efforts should not last longer than 1–2 hours between puppies, although
great variation exists. The entire delivery can take between 1 and > 24 hours; however, normal labor is
associated with shorter total delivery time and shorter intervals between neonatal births. Vaginal
discharge can be clear, serous to hemorrhagic, or green (uteroverdin). Typically bitches continue to nest
between deliveries, and may nurse and groom neonates intermittently. Anorexia, panting and trembling
are common.

Stage III labor is defined as the delivery of the placenta. Bitches typically vacillate between stages II
and III of labor until the delivery is complete. During normal labor, all fetuses and placentae are
delivered vaginally, although they may not be delivered together in every instance.

The stages of labor in the queen can be similarly defined. Stage 1 labor in the queen is reported to
last 4–24 hours and stages II and III from 2 to 72 hours, although completion of delivery of neonates
within 24 hours is expected with normal queening.

Dystocia results from maternal factors (uterine inertia, pelvic canal anomalies, intrapartum
compromise), fetal factors (oversize, malposition, malposture, anatomic anomalies), or a combination of
both. For effective management, the recognition of dystocia must be made in a timely manner, and
identification of etiologic factors made correctly.

Uterine inertia is the most common cause of dystocia. Primary uterine inertia results in the failure
of delivery of any neonates at term and is thought to be multifactorial, including metabolic defects at
the cellular level. An intrinsic failure to establish a functional, progressive level of myometrial
contractility occurs. A genetic component may be present. Secondary uterine inertia results in the
cessation of labor once initiated and consequential failure to deliver the entire litter. Secondary inertia
can result from metabolic or anatomic (obstructive) causes, and is also thought to have a genetic
component. Birth canal abnormalities such as vaginal strictures, stenosis from previous pelvic trauma or
particular breed conformation, and intravaginal or intrauterine masses can cause obstructive dystocia.
In most cases, canal abnormalities can be detected in the pre-bredding examination and can be resolved
or avoided by elective cesarean section. Causes of intrapartum compromise rendering the dam unable
to complete delivery include metabolic abnormalities such as hypocalcemia and hypoglycemia, systemic
inflammatory reaction, sepsis, and hypotension (due to hemorrhage or shock).

Fetal factors contributing to dystocia most commonly involve mismatch of fetal and maternal size,
fetal anomalies and fetal malposition and/or malposture. Prolonged gestation with small litter size can
cause dystocia due to an oversized fetus(es). Fetal anomalies such as hydrocephalus and anasarca
similarly can cause dystocia. Fetal malposition (ventrum of fetus proximal to the dam’s dorsum) and
fetal malposture (flexed neck and scapulohumeral joints most commonly) promote dystocia as the fetus
cannot transverse the birth canal smoothly.

An efficient diagnosis of dystocia is dependent upon taking an accurate history and performing a
thorough physical examination in a timely manner. The clinician must quickly obtain a careful
reproductive history detailing breeding dates, any ovulation timing performed, historical and recent
labor, as well as a general medical history. The physical examination should address the general status
of the patient, as well as include a digital and/or vaginoscopic pelvic exam for patency of the birth canal,
evaluation of litter and fetal size (radiography most useful), assessment of fetal viability (Doppler or real-
time ultrasound ideally) and uterine activity (tocodynamometry most useful).

A novel approach to veterinary obstetrical monitoring in use in the United States involves the use of
external monitoring devices using tocodynamometry (Healthdyne Inc., Marietta, GA, USA) and a
handheld Doppler (Sonicaid, Oxford Instruments, England) to detect and record uterine activity and fetal
heart rates. These devices can be used either in the home setting or at the veterinary clinic. Their use
requires that the hair coat be lightly clipped caudal to the ribcage, over the gravid area of the lateral
flanks, to allow proper contact of the uterine sensor and fetal Doppler. The uterine sensor detects
changes in intrauterine and intra-amniotic pressures. The sensor is strapped over the lightly clipped area
of the bitch’s/queen’s caudolateral abdomen using an elasticized strap. The sensor’s recorder is worn in a small backpack placed over the caudal shoulder area. Bitches/queens are at rest in the whelping/queening box or in a crate or cage during the monitoring sessions. The monitoring equipment is well tolerated. Subsequent to each recording session, data is transferred from the recorder via a modem using standard telephones. Fetal Doppler monitoring is performed bilaterally with a handheld unit with bitches/queens in lateral recumbency, using acoustic coupling gel. Directing the Doppler perpendicularly over a fetus results in a characteristic amplification of the fetal heart sounds, distinct from maternal arterial or cardiac sounds, which enables determination of fetal heart rates.

Interpretation of the contractile pattern in strips produced by the uterine monitor requires training and experience. Data is transferred by modem to obstetrical personnel capable of interpretation, who subsequently consult with the attending veterinary clinician and client. Recordings are made on a twice-daily, hour-long basis when home monitoring is performed, then intermittently on bitches or queens at home as indicated during active labor, or on site in the veterinary clinic for shorter periods of time (minimally 20 minutes) when patients are being evaluated for suspected dystocia.

The canine and feline uterus each has characteristic patterns of contractility, varying in frequency and strength before and during the different stages of labor.

Serial tocodynamometry in the bitch and queen permits evaluation of the progression of labor. During late term, the uterus may contract once or twice an hour before actual stage I labor is initiated. During stage I and II labor, uterine contractions vary in frequency from 0 to 12 per hour, and in strength from 15 to 40 mm Hg, with spikes up to 60 mm Hg. Contractions during active labor can last 2 to 5 minutes in duration. Recognizable patterns exist during prelabor and active (stages 1–3) labor. Aberrations in uterine contractility can be detected during monitoring. Abnormal, dysfunctional labor patterns can be weak or prolonged and often are associated with fetal distress. Additionally, the completion of labor (or lack thereof) can be evaluated via tocodynamometry.

Figure 1. Graph of uterine monitoring recordings, mm Hg vs. time in minutes. Normal baseline myometrial tracing, no contractions, prelabor. Variation off baseline at attachment of sensor (1–2 minutes).
Figure 2. Early active labor, stage II, uterine contractions and abdominal pushing
Caption: “C” = contraction

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Figure 3. Active labor, abdominal pushing with uterine inertia
Caption: Vertical spikes (c) indicate abdominal efforts.
Figure 4. Same bitch as in Figure 3, treated with 6 ml 10% calcium gluconate SC and 0.50 USP u oxytocin IM. Abdominal pushing evident in conjunction with uterine contractions ©. Puppy was delivered in 26 minutes.

Figure 5. Empty postpartum uterus
The presence of fetal distress is reflected by sustained deceleration of the heart rates. Normal canine and feline fetal heart rates at term are from 170 to 230 beats per minute (bpm), or at least $4 \times$ the maternal heart rate. In the periparturient period, the cardiac output of the fetus/neonate is mainly dependent on heart rate as the right ventricle is relatively stiff (low compliance) and the autonomic nervous system is immature (minimal inotropic response to catecholamines). Decelerations associated with uterine contractions suggest mismatch in size between the fetus and dam, or fetal malposition or malposition. Transient accelerations occur with normal fetal movement. Fetal heart rates of ≤ 150 to 160 bpm indicate stress. Fetuses with heart rates ≤ 130 bpm have poor survival if not delivered within 2 to 3 hours, and fetuses with heart rates ≤ 100 bpm are an indication for immediate intervention to hasten delivery (medical or surgical) before their demise.

The use of uterine and fetal monitors allows the veterinary clinician to detect and monitor labor, as well as manage labor medically or surgically with insight instead of guesswork. At Guide Dogs for the Blind, Inc., the overall stillbirth rate declined from 9.2% to 2.5% with incorporation of uterine and fetal monitoring into the whelping process. Medical therapy for dystocia, based on the administration of oxytocin and calcium gluconate, can be directed and tailored based on the results of monitoring. Generally, the administration of oxytocin increases the frequency of uterine contractions, while the administration of calcium increases their strength. Oxytocin, 10 USP u/ml (American Pharmaceutical Partners, Inc., Los Angeles, CA, USA) is effective at mini doses, starting with 0.25 units SC or IM to a maximum dose of 4 units per bitch or queen. Higher doses of oxytocin or intravenous boluses can cause tetanic, ineffective uterine contractions that can further compromise fetal oxygen supply by placental compression. The frequency of oxytocin administration is dictated by the labor pattern, and it is generally not given more frequently than hourly. Calcium gluconate 10% solution with 0.465 mEq Ca++/ml (Fujisawa, Inc., USA) is given SC at 1 ml/5.5 kg BW as indicated by the strength of uterine contractions, generally no more frequently than every 4–6 hours. Calcium is given before oxytocin in most cases, improving contraction strength before increasing frequency. Additionally, the action of oxytocin appears to be improved when given 15 minutes subsequent to calcium. Most bitches/queens are eucalcemic, suggesting that the benefit of calcium administration is at a cellular or subcellular level.

Surgical intervention (cesarean section) is indicated if a bitch or queen fails to respond to medical management, or if fetal distress is evidenced despite adequate to increased uterine contractility (suggesting mismatch of maternal birth canal to fetal size, or fetal malposition or malposition
incompatible with vaginal delivery), or if aberrant contractile patterns are noted by uterine monitoring. Well-orchestrated cesarean sections result when anesthetic and neonatal resuscitative protocols are established and coordinated, and the preoperative preparation of the dam optimized. It should always be remembered that the dam may be debilitated and require careful anesthetic management, there may be little time for routine preanesthetic preparation, and the dam may have been fed recently. Minimally, the hematocrit, total solids, serum calcium and glucose levels should be evaluated preoperatively. Intravenous fluid support at an operative rate minimally is indicated (10 ml/kg/h).

For premedication, atropine is best not given routinely, because it crosses the placenta and blocks the normal, adaptive bradycardic response of the fetus to hypoxia and causes relaxation of the lower esophageal sphincter, making maternal aspiration more likely. However, the use of an anticholinergic is indicated for the dam because of the anticipated vagal stimulation during manipulation of the gravid uterus. Glycopyrrolate (0.01–0.02 mg/kg SC) does not cross the placenta and is preferred. Most dams are tractable and do not need preanesthetic tranquilization, which has a depressant effect on the fetuses. Phenothiazine tranquilizers are transported rapidly across the placenta and are depressants. Alpha2-adrenoceptor agonists such as dexmedetomidine and xylazine are contraindicated because of their severe cardiorespiratory depressant effects. Similarly, the respiratory depressant effect of opioids makes them unpopular prior to removal of the fetuses. If tranquilization is necessary with an intractable dam, narcotic sedatives are preferable, as their effects can be reversed (naloxone 1–10 µg/kg IV or IM) during neonatal resuscitation. Metoclopramide (0.10–0.20 mg/kg) can be administered subcutaneously or intramuscularly prior to the induction of anesthesia to reduce the risk of vomiting during the procedure.

Preoxygenation by mask (5–10 minutes) is always indicated. Initial preparation of the abdomen (clipping and first scrubbing) can be undertaken during this time. For induction of anesthesia, dissociative agents such as ketamine and the barbiturates are best avoided, because they produce profound depression of the fetuses. Propofol (6 mg/kg IV to effect) appears to be most useful; because of its rapid redistribution, it therefore has a limited effect upon the fetuses after delivery. Mask induction actually produces more maternal and fetal hypoxemia than propofol induction. For maintenance of anesthesia, volatile agents are preferable, especially those with low partition coefficients such as isoflurane and sevoflurane. These agents show rapid uptake and elimination by the animal, and it may have a better cardiovascular margin of safety than the more soluble agents such as halothane. Nitrous oxide may be used to reduce the dose of other anesthetic agents; it is transferred rapidly across the placenta and, although it has minimal effects upon the fetus in utero, it may result in a significant diffusion hypoxia after delivery. Using a local anesthetic (bupivacaine 2 mg/kg) line block in the skin and subcutaneous tissues prior to incising permits a more rapid entry to the abdomen while the dam is making transition from propofol induction to inhalant maintenance, and it helps with postoperative discomfort.

Operative speed is important, because surgical delay and prolonged anesthetic time are associated with fetal asphyxia and depression. However, care should be taken during incision of the linea alba to ensure that the gravid uterus is not also incised. Ideally, the uterus should be exteriorized and packed off with moistened laparotomy sponges to prevent abdominal contamination with uterine fluid. This process should be undertaken carefully to ensure that the uterus and its broad ligament do not tear; it may be easier in some cases to exteriorize one horn at a time. The uterus should be penetrated in a relatively avascular area, and it is best to elevate the uterine wall from the fetus and to extend the incision with scissors to ensure that the fetus is not lacerated. The fetuses may be brought to the incision by gently ‘milking’ them along the uterus, although in some cases or in large dams, it may be necessary to make more than one incision. As the fetal fluid is released, it is best to remove this by suction and then to clamp the umbilicus (twice, incising between clamps) before passing the fetus to an
assistant for immediate resuscitation. After each fetus is removed, the associated placenta should be detached by gentle traction, but the placentas may be left in situ if they are firmly attached and their removal causes significant hemorrhage. Placentas can be spontaneously passed postoperatively or managed medically. It is essential that the uterine horns, the uterine body and the vagina are inspected thoroughly to ensure that all fetuses have been removed. Finally, after closure the uterus, its broad ligament and the vascular supply should be inspected carefully to ensure that any previously unnoticed tears have been identified before closure of the abdomen. Ovariohysterectomy at the time of cesarean section is again the option of the surgeon and owner, but it results in longer anesthetic time for the dam, delayed nursing for the neonates, and increased loss of blood in the dam, so it should be postponed if reasonable. There is some belief that estrogen acts in a permissive fashion for prolactin receptors in the mammary glands, making ovary removal at cesarean section undesirable. If uterine viability is questionable, an ovariohysterectomy should be performed. In the normal dam, the uterus will begin to involute shortly after removal of the fetuses, but if this is not the case, oxytocin may be administered (0.25–1.0 u per dam) to facilitate involution and arrest any hemorrhage; this also promotes milk letdown.

Postoperative discomfort should be acknowledged in the dam. Once the fetuses are removed, narcotic analgesia can be administered parenterally to the dam. Postoperatively, nonsteroidal antiinflammatory agents are not advisable due to their uncertain metabolism by the nursing neonates with immature renal and hepatic metabolism. Narcotic analgesia is preferable. Oral narcotics such as tramadol, 10 mg/kg/day in divided doses, provide excellent postoperative analgesia for nursing bitches with minimal sedation of the neonates. In all cases, clients should be advised to closely monitor bitches postoperatively until normal maternal behavior emerges. Post cesarean section, bitches can be clumsy and inattentive to the neonates and can even become aggressive, as the normal mechanisms of maternal bonding have been bypassed. Nursing should be supervised and neonatal care ensured.

**Immediate Postpartum Period**

Normally, dams stay very close to their offspring during the first 2 weeks postpartum, leaving the whelping/queening box briefly, if at all, to eat and eliminate. They are alert and content to remain with their offspring. Some protective dams may show aggression to housemate animals or even people with whom they are normally tolerant; such behavior tends to dissipate after 1–2 weeks of lactation. Lactation typically presents the greatest nutritional and caloric demand of the female’s life. Weight loss and dehydration may occur and impact lactation if food and water are not made readily available; sometimes this entails leaving both in the nest box with a nervous dam. Partial anorexia can be exhibited during the last weeks of gestation and in the immediate postpartum period, but the appetite should return and increase as lactation progresses. Poor appetite during the last weeks of gestation can be due to displacement of the gastrointestinal tract by the gravid uterus. Partial anorexia early in the postpartum period can occur secondary to digestive upset following the consumption of numerous placentae. Diarrhea can occur secondary to increased rations and rich food (bacterial overgrowth secondary to carbohydrate malassimilation). Marked postpartum effluvia is normal in the bitch, usually occurring at 4–6 weeks after whelping, and sparing only the head. This is usually more marked than that which occurs in conjunction with the typical estrous cycle, and can be interpreted as pathologic by an owner, especially in conjunction with the weight loss typically associated with lactation. The body temperature of the dam may be mildly elevated (< 103.0 degrees F) in the immediate postpartum period, reflecting anticipated normal inflammation associated with parturition, but it should return to normal levels within 24–48 hours. If a cesarean section took place, differentiating normal postsurgical inflammation from fever associated with pathology may be difficult. The physical examination and a complete hemogram help the clinician differentiate between the two. Normal
postpartum lochia is brick-red in color, nonodorous, and diminishes over several days to weeks (uterine involution and repair occur for up to 16 weeks in the bitch). The mammary glands should not be painful; rather they are symmetric and moderately firm without heat, erythema, or palpable firm masses. If expressed, normal milk is grey to white in color and of watery consistency.

**CLINICAL PROBLEMS**

**Inappropriate Maternal Behavior**

Appropriate maternal behavior is critical to neonatal survival and includes attentiveness, facilitation of nursing, retrieving neonates, grooming and protecting neonates. Although maternal behavior is instinctual, it can be negatively influenced by anesthetic drugs, pain, stress, and excessive human interference. Maternal bonding is a pheromone-mediated event initiated at parturition. Whelping and queening should take place in quiet, familial surroundings, with minimal human interference, yet adequate supervision. Dams with good maternal instincts exhibit caution when entering or moving about the nest box so as not to traumatize neonates by stepping or lying on them. A guardrail along the inside of the whelping box prevents inadvertent smothering of canine neonates.

The neuroendocrine reflex regulating mammary gland myoepithelial cell contraction and subsequent milk ejection is mediated by oxytocin and activated by neonatal suckling. During stress, epinephrine induces vasoconstriction, blocking the entry of oxytocin into the mammary gland and preventing milk ejection. A nervous, agitated dam will likely have poor milk availability. Dopamine antagonist tranquilizers, with minimal prolactin interference (acepromazine 0.01–0.02 mg/kg) administered at the lowest effective dose to minimize neonatal sedation, can improve maternal behavior and mild ejection in nervous dams. Piling of littermates near their dam facilitates the maintenance of their adequate body temperature (neonates cannot thermoregulate/shiver for up to 4 weeks of age) and makes nursing readily available. Normal maternal behavior includes gentle retrieval of neonates who have become dispersed and isolated across the nest box. Grooming of the neonates immediately following parturition stimulates their cardiovascular and pulmonary function and removes amniotic fluids. Dams demonstrating little interest in resuscitating neonates can have poor maternal behavior throughout the postnatal period. Later, maternal grooming stimulates reflex neonatal urination and defecation and maintains the neonatal coat in a clean, dry state. Occasionally, excessive protective behavior or fear-induced maternal aggression can occur. Mild tranquilization of the dam with an anti-anxiety agent can help, but neonatal drug administration via the milk can be problematic. Benzodiazepines, GABA synergists, are reportedly superior to phenothiazines for fear-induced aggression (diazepam 0.55–2.2 mg/kg). The role of newer anti-anxiety pharmaceuticals in maternal aggression has not been described in a controlled setting.

**Uterine Disorders**

Complete or partial prolapse of the uterus is an uncommon postpartum condition in the bitch, occurring rarely in the queen. The diagnosis is based on palpation of a firm, tubular mass protruding from the vulva postpartum and inability to identify the uterus with abdominal ultrasonography. Vaginal hyperplasia and prolapse, secondary to a hypersensitivity of focal (periurethral) vaginal mucosa to estrogen, can recur near parturition and should be ruled out by physical examination, vaginoscopy, or contrast radiography. The prolapsed uterine tissues are at risk for maceration and infection from exposure and contamination. The size of most bitches and queens precludes manual replacement; laparotomy and ovariohysterectomy are usually indicated.

Rupture of the uterus occurs most commonly with very large litters causing marked stretching and thinning of the uterine wall, especially in multiparous dams with dystocia. Immediate laparotomy for retrieval of fetuses and repair or removal of the uterus, as well as culture and lavage of the abdominal
cavity, is indicated. The uterus should be carefully examined at any cesarean section for any areas with or prone to rupture. Peritonitis can result from an undetected uterine tear. A unilateral hysterectomy can be considered if the damaged area is limited and the dam is valuable to a breeding program.

The persistence of serosanguineous to hemorrhagic vaginal discharge beyond 16 weeks postpartum can indicate subinvolution of the placental sites of attachment (SIPS) in the bitch. Histologically, fetal trophoblastic cells have persisted in the myometrium instead of degenerating, endometrial vessel thrombosis is lacking, and normal involution of the uterus is prevented. Normal interplacental regions exist. Eosinophilic masses of collagen and dilated endometrial glands protrude into the uterine lumen, oozing blood. The cause is unknown, blood loss is usually minimal, intrauterine infection not present, and fertility is unaffected. Treatment is generally not necessary, as recovery is spontaneous and symptoms mild. In the uncommon situation where vaginal bleeding from SIPS is copious enough to cause serious anemia, coagulopathies (likely defects in the intrinsic pathway or thrombocytopenia/thrombocytopenias), trauma, neoplasia of the genitourinary tract, metritis and proestrus should be ruled out. Vaginal cytology, vaginoscopy, coagulation testing and abdominal ultrasound assist in the diagnosis. Treatment in these cases can be attempted with ergonovine (0.2 mg/15 kg IM) administered once or twice. The benefit of therapeutic prostaglandins and/or oxytocin is questionable and not proven in any controlled study. The preventative value of oxytocin given in the immediate postpartum period is also unproven. Laparotomy and ovariohysterectomy are curative. Histologic examination of the uterus is indicated to confirm the diagnosis.

Acute infection of the postpartum endometrium should be suspected if lethargy, anorexia, decreased lactation and poor mothering occur accompanied by fever and malodorous vaginal discharge. Metritis is serious and sometimes preceded by dystocia, contaminated obstetrical manipulations, or retained fetuses and/or placentae. Hematologic and biochemical changes often suggest septicemia, systemic inflammation reaction and endotoxemia. Vaginal cytology shows a hemorrhagic to purulent septic discharge. Ultrasound of the abdomen allows evaluation of intrauterine contents and the uterine wall. Retained fetuses and placentae can also be identified with ultrasound. A guarded cranial vaginal culture is likely representative of intrauterine flora and should be submitted for both aerobic and anaerobic culture and sensitivities, and it permits retrospective assessment of empirically selected antibiotic therapy. Bacterial ascension from the lower genitourinary tract is more common than hematogenous spread, and *Escherichia coli* is the most common causative organism in both bitches and queens. Therapy consists of intravenous fluid and electrolyte support, appropriate bactericidal antibiotic administration and pharmacologic uterine evacuation, usually with prostaglandin F2 alpha (in the United States) at a dose of 0.10–0.20 mg/kg q 12–24 h for 3–5 days. An ovariohysterectomy may be indicated if the bitch’s condition permits, and she is poorly responsive to medical management. Ergonovine (0.2 mg/15 kg given once IM) is also an effective ecbolic agent, but it may cause rupture of a friable uterine wall. Synthetic prostaglandins offer more uterine-specific therapy where available. Oxytocin is unlikely to promote effective uterine evacuation when administered > 24–48 hours postpartum. Nurslings should be hand-reared if the dam is seriously sick. Metritis can become chronic and cause infertility.

**Mammary Disorders**

Agalactia is defined as a failure to provide milk to neonates. Primary agalactia, a lack of mammary development during gestation, results from a failure of milk production and is uncommon. A defect in the pituitary ovarian mammary gland axis is suspected. The use of progesterone compounds late in gestation can interfere with lactation. Secondary agalactia, a lack of milk availability due to a failure of ejection, is more common. Mammary development is marked, but milk cannot be readily expressed through the teat sphincter. The normal production of colostrum in the immediate postpartum period should not be confused with agalactia. Agalactia can occur secondary to premature parturition, severe
stress, malnutrition, debility, metritis, or mastitis. Treatment includes providing supplementation to the neonates while encouraging suckling to promote milk ejection, providing optimal levels of nutrition and adequate water to the dam, and resolution of any underlying disease. If detected early, milk letdown can often be induced pharmacologically. Mini dose oxytocin, 0.25–1.0 units per injection, is given subcutaneously every 2 hours. Neonates are removed for 30 minutes post injection and then encouraged to suckle, or gentle stripping of the glands is performed. Metoclopramide, 0.1–0.2 mg/kg SC is given q 12 h (dopamine antagonist) to promote milk production. Therapy is usually rewarding within 24 hours. Some authors advise a much higher dose of metoclopramide, but neurologic side effects become possible.

Galactostasis can cause engorgement and edema of the mammary gland with associated discomfort, making further nursing unlikely, and becoming self-perpetuating. Galactostasis occurs secondary to inverted or imperforate teats, failure to rotate nurslings, litter loss, an unusually small litter, or rarely with pseudocyesis.

Mastitis, septic inflammation of the mammary gland, can be acute and fulminate or chronic and low grade, involving a single or multiple mammary glands. Coliforms, staphylococci, and streptococci are most commonly isolated in both bitches and queens. The source of bacteria is cutaneous, exogenous or hematogenous. Mild mammary discomfort and heat, galactostasis, cutaneous inflammation, and the presence of an intramammary mass are the earliest signs. Milk is commonly discolored red or brown due to the presence of red and white blood cells. Moderate cases exhibit pain, reluctance to nurse or lie down, anorexia and lethargy. Fever can be marked and may precede other clinical signs. Advanced cases can present in septic shock, with abscessed or necrotic glands. The diagnosis is based upon physical examination. Milk cell counts in bitches are not predictive of mastitis. Culture and sensitivity of milk collected aseptically from affected glands allows retrospective evaluation of antibiotic selection. Therapy should begin immediately, consisting of broad-spectrum, bactericidal antimicrobials and gentle physical therapy. Analgesics may be indicated; neonates tolerate opioid analgesia in the dam. First-generation cephalosporins (cephalexin 10–20 mg/kg q 8–12 h) and beta lactamase-resistant penicillins (Clavamox 14 mg/kg q 12 h) are advised and safe for the neonates. Antibiotic therapy may be warranted until weaning and can preclude further nursing if sensitivities force the choice of a drug potentially toxic to neonates. Warm compresses or whirlpool therapy of the affected gland with gentle stripping of milk can potentially avert abscessation and rupture of the gland. Severe necrosis warrants mastectomy (when the dam is stabilized) and aggressive wound management. Anti-prolactin therapy (cabergoline 1.5–5.0 µg/kg/day divided BID) may be indicated in severe cases to reduce lactation. There is no evidence that nursing from affected glands is problematic for neonates, but they tend to avoid glands which are difficult to obtain milk from. The affected gland should be protected from trauma from nest box edges and neonatal claws. Mastitis can recur in subsequent lactations regardless of preventative measures taken. Early detection and treatment are optimal, rather than prophylactic antibiotics, which tend to favor resistant organisms.

ENDNOTE

a. VPI - Veterinary Perinatal Specialties, Inc., 9111 W. 38th Ave., Wheat Ridge, CO 80033, USA; (303) 423 3429; Fax: (303) 423 8242; email wlpwise@aol.com
Canine and Feline Neonatal Resuscitation: Techniques to Improve Outcome
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Average reported neonatal mortality rates (greatest during the first week of life) vary, ranging from 9–26%. Prudent veterinary intervention in the prenatal, parturient and postpartum periods can increase neonatal survival by controlling or eliminating factors contributing to puppy morbidity and mortality. Poor prepartum condition of the dam, dystocia, congenital malformations, genetic defects, injury, environmental exposure, malnutrition, parasitism and infectious disease all contribute to neonatal morbidity and mortality. Optimal husbandry impacts neonatal survival favorably by managing labor and delivery to reduce stillbirths, controlling parasitism and reducing infectious disease, preventing injury and environmental exposure, and optimizing nutrition of the dam and neonates. Proper genetic screening for selection of breeders minimizes inherited congenital defects. The neonatal period can be divided into the prepartum (prenatal) period, parturition, and the postpartum neonatal period; we will focus on the latter here.

Optimal neonatal resuscitation following birth (if the dam fails to do so) or caesarean section involves the same “A-B-Cs” as any cardiopulmonary resuscitation. First, prompt clearing of airways (“A”) by gentle suction with a bulb syringe; drying and stimulation of the neonate to promote respiration (“B”); and avoiding of chilling are performed. Neonates should not be swung to clear airways, as described in the veterinary literature, because of the potential for cerebral hemorrhage from concussion. The use of doxapram as a respiratory stimulant is unlikely to improve hypoxemia associated with hypoventilation, and it is not recommended. Spontaneous breathing and vocalization at birth are positively associated with survival through 7 days of age. Intervention for resuscitation of neonates following vaginal delivery should take place if the dam’s actions fail to stimulate respiration, vocalization, and movement within one minute of birth.

Cardiopulmonary resuscitation for neonates who fail to breathe spontaneously is challenging, yet potentially rewarding. Ventilatory support should include constant-flow O2 delivery by facemask. If this is ineffective after one minute, positive pressure with a snugly fitting mask or endotracheal intubation and rebreathing bag (using a 2-mm endotracheal tube or a 12- to 16-gauge intravenous catheter) is advised. Anecdotal success with Jen Chung acupuncture point stimulation has been claimed when a 25-gauge needle is inserted into the nasal philtrum at the base of the nares and rotated when bone is contacted. Cardiac stimulation (“C”) should follow ventilation support, as myocardial hypoxemia is the most common cause of bradycardia or asystole. Direct transthoracic cardiac compressions are advised as the first step; epinephrine is the drug of choice for cardiac arrest/standstill (0.2 mg/kg administered best by the intravenous or intraosseous route). Venous access in the neonate is challenging; the single umbilical vein is one possibility. The proximal humerus, proximal femur and proximo-medial tibia offer intraosseous sites for drug administration. Atropine is currently not advised in neonatal resuscitation. The mechanism of bradycardia is hypoxemia-induced myocardial depression rather than vagal mediation, and anticholinergic-induced tachycardia can actually exacerbate myocardial oxygen deficits.

Beyond the ABCs
Chilled neonates can fail to respond to resuscitation. Loss of body temperature occurs rapidly when a neonate is damp. Keeping the neonate warm is important during resuscitation and in the immediate postpartum period. During resuscitation, placing the chilled neonate’s trunk into a warm-water bath
(95–99°F) can improve response. Working under a heat lamp or within a Bair hugger warming device is helpful. Post resuscitation, neonates should be placed in a warm box (a Styrofoam picnic box with ventilation holes is ideal) with warm bedding until they can be left with their dam.

Neonates lack glucose reserves and have minimal capacity for gluconeogenesis. Providing energy during prolonged resuscitation efforts becomes critical. Clinical hypoglycemia involves blood glucose levels less than 30 to 40 mg/dl, and it can be treated with dextrose solution intravenously/intraosseously, at a dose of 0.5 to 1.0 g/kg using a 5% to 10% solution, or a dose of 2 to 4 ml/kg of a 10% dextrose solution. Single administration of parenteral glucose is adequate if the puppy can then be fed or nurses. Fifty percent dextrose solution should only be applied to the mucous membranes because of the potential for phlebitis if administered intravenously; however, circulation must be adequate for absorption from the mucosa. Neonates administered dextrose should be monitored for hyperglycemia because of immature metabolic regulatory mechanisms. If a neonate is too weak to nurse or suckle, a mixture of a warmed, balanced crystalloid (lactated Ringer’s solution or Normosol solution) and 5% dextrose may be administered subcutaneously at a dose of 1 ml per 30 g of bodyweight, until the pup can be fed or nurses. A balanced, warmed nutrient-electrolyte solution can be administered orally by stomach tube every 15–30 minutes until the neonate is capable of suckling.

**When to Stop Resuscitation**
- No response after 15–20 minutes of effort (continued agonal respiration, bradycardia)
- Serious congenital defect detected (cleft palate, loud murmur, gastroschisis, large omphalocele, large fontanel)

**HUSBANDRY: THE FIRST DAYS**
Post resuscitation or within the first 24 hours of a natural delivery, a complete physical examination should be performed by a veterinarian, technician, or knowledgeable breeder. The oral cavity, hair coat, limbs, umbilicus and urogenital structures should be visually inspected. The mucous membranes should be pink and moist, a suckle reflex present, the coat full and clean, the urethra and anus patent. A normal umbilicus is dry without surrounding erythema. The thorax should be ausculted; vesicular breath sounds and a lack of murmur are normal. The abdomen should be pliant and not painful. A normal neonate will squirm and vocalize when examined, nurse and sleep quietly when returned to the dam. Normal neonates will attempt to right themselves and orient by rooting toward their dam. Neonates are highly susceptible to environmental stress, infection, and malnutrition. Proper husbandry is critical and should include daily examination of each neonate for vigor and recording of weight.

**Warmth**
Puppies lack thermoregulatory mechanisms until four weeks of age; thus, the ambient temperature must be high enough to facilitate maintenance of a body temperature of at least 97°F (36°C). Hypothermia negatively impacts immunity, nursing, and digestion. Exogenous heat should be supplied, best in the form of an overhead heat lamp. Heating pads run the risk of burning neonates incapable of moving away from excessively hot surfaces.

**Neonatal normal body temperature (rectal)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>95–99°F</td>
</tr>
<tr>
<td>Week 2–3</td>
<td>97–100°F</td>
</tr>
<tr>
<td>At weaning</td>
<td>99–101°F</td>
</tr>
</tbody>
</table>
**Environmental warmth required**

<table>
<thead>
<tr>
<th>Week</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>84–89°F</td>
</tr>
<tr>
<td>Weeks 2/3</td>
<td>80°F</td>
</tr>
<tr>
<td>Week 4</td>
<td>69–75°F</td>
</tr>
<tr>
<td>Week 5</td>
<td>69°F</td>
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</table>

Chilled neonates must be rewarmed slowly (30 minutes) to avoid peripheral vasodilation and dehydration. Tube feeding should be delayed until the neonate is euthermic; hypothermia induces ileus, and regurgitation and aspiration can result.

**Immunity**

Incomplete immune systems during the first 10 days of life make neonates vulnerable to systemic infection (most commonly bacterial and viral). Adequate ingestion of colostrum must occur promptly postpartum for puppies to acquire passive immunity. The intestinal absorption of IgG generally ceases by 24 hours after parturition. Colostrum-deprived kittens given adult cat serum at a dose of 150 ml/kg SC or IP developed serum IgG levels comparable with suckling littermates; however, colostrum-deprived puppies given 40 ml/kg adult dog serum orally and parenterally failed to match suckling littermates’ IgG levels. Neonates should be encouraged to suckle promptly after resuscitation is completed; this usually necessitates close monitoring after a caesarean section, as the dam is still groggy from anesthesia. Replacement serum or plasma can be given orally within the first 24 h of life or parenterally (SC or IP) after 24 h of life at a dose of 0.10 ml/gm bodyweight. Maternal instincts (protecting, retrieving, grooming, nursing) usually return within 24 hours.

The umbilicus of neonates should be treated with tincture of iodine immediately after birth to reduce contamination and prevent ascent of bacteria into the peritoneal cavity (omphalitis-peritonitis).

Neonatal bacterial septicemia can cause rapid deterioration, resulting in death if not recognized and treated promptly. Factors that reportedly predispose a puppy to septicemia include endometritis in the bitch, a prolonged delivery/dystocia, feeding of replacement formulas, the use of ampicillin, stress, low birthweight (< 350 g for a medium-size breed), and chilling with body temperature < 96°. The organisms most frequently associated with septicemia are *E. coli*, streptococci, staphylococci, and *Klebsiella* spp. Premortem diagnosis can be challenging; clinical signs may not be noted due to sudden death. Commonly, a decrease in weight gain, failure to suckle, hematuria, persistent diarrhea, unusual vocalization, abdominal distension and pain, and sloughing of the extremities indicate septicemia may be present. Prompt therapy with broad-spectrum, bactericidal antibiotics; improved nutrition via supported nursing, tube feeding, or bottle feeding; maintenance of body temperature; and appropriate fluid replacement are indicated. The third-generation cephalosporin antibiotic, ceftiofur sodium (Naxcel; Pharmacia and Upjohn), is an appropriate choice for neonatal septicemia, as it alters normal intestinal flora minimally and is usually effective against the causative organisms. Ceftiofur sodium should be administered at a dose of 2.5 mg/kg SC q 12 h for no longer than 5 days. Because puppies less than 48 hours old have reduced thrombin levels, presumptive therapy with vitamin K1 may be used (0.01–1.0 mg SC per puppy).

**Groceries**

Neonates have minimal body fat reserves and limited metabolic capacity to generate glucose from precursors. Glycogen stores are depleted shortly after birth, making adequate nourishment from nursing vital. Even minimal fasting can result in hypoglycemia. Hypoglycemia can also result from endotoxemia, septicemia, portosystemic shunts, and glycogen storage abnormalities. Oral fluid and glucose
replacement may be preferable if the puppy has an adequate swallowing reflex and is not clinically compromised. The neonatal caloric requirement is 133 calories/kg/day during the first week of life, 155 calories/kg/day for the second, 175–198 calories/kg/day for the third, and 220 calories/kg/day for the fourth. Commercially manufactured milk replacement formulas (Esbilac - Pet-Ag Inc., Elgin, IL; Puppy Milk Replacer Formula: Eukanuba, The Iams Co., Dayton, OH; Veta-Lac Powder for Puppies: Vet-A-Mix, Shenandoah, IA, KMR- Pet-Ag Inc., Elgin, IL) are usually superior to homemade versions. The use of milk obtained from the dam can be considered, if available. An osmotic diarrhea (usually yellow, curdled stool appearance) can result from overfeeding formula, necessitating diluting the product 50% with water or a balanced crystalloid such as lactated Ringer’s solution. Neonates should gain weight steadily from the first day after birth (a transient mild loss from birthweight is acceptable on day 1); puppies gaining 1–3 grams per day per pound (2.2 kg) of anticipated adult weight, and kittens 50–100 grams weekly. Neonatal weights should be recorded daily for the first two weeks, then every 3 days until a month of age. Healthy, well-nourished neonates are quiet and sleep when not nursing.

Normal Neonatal Weight Gain
Increase of 5–10% bodyweight per day

Table 1. Neonatal resuscitation kit
- Syringes (tb), acupuncture needles or 28 G needles
- Epinephrine freshly diluted to 1:1000, 50% dextrose freshly diluted to 2.5–5%
- Oxygen sources
- Suction (pediatric bulb syringes, Dee aspirators)
- Small face masks
- Towels (smallish and lots of them)
- Heat source (Baer, warm-water blanket, infrared lamp)
- Puppy box (Styrofoam) with heat support
- Multiple clean mosquito forceps and small scissors
- 3-0 gut suture for umbilical cords needle removed, cut in 5” lengths
- Tincture of iodine
- Bowls for warm-water baths
- Pediatric/neonatal stethoscope
- Doppler
- Neonatal scale

Neonatal Resuscitation Drugs
- Dilute epinephrine
- Dilute dextrose
- Ceftriaxone
- Vitamin K1
- Narcotic reversal
Obstetrical Emergencies
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The periparturient period can be associated with high morbidity and even mortality for the dam and neonates. The periparturient period is defined here as the immediate prepartum period (1–2 weeks before parturition) and the 30- to 45-day postpartum period before weaning. The diagnosis of periparturient problems first requires their recognition and differentiation from normal situations; effective treatment depends on both a timely diagnosis and therapeutic intervention.

Premature Labor
Late-term gestational loss attributed to preterm or premature labor is a controversial topic in small animal reproduction. Both hypoluteoidism and inappropriate uterine activity accompanied by cervical changes have been implicated in the pathophysiology of preterm birth in veterinary medicine, but the syndrome is not well understood or even researched. While the human literature is abundant on the topic, publications on the topic are few in veterinary medicine.

Premature labor is defined here as uterine activity and cervical changes leading to the loss of pregnancy via resorption or abortion before term, for which no metabolic, infectious, congenital, traumatic or toxic cause is identified. Premature labor is associated with progesterone levels that are < 2 ng/ml. Premature labor is often a retrospective diagnosis, achieved after thorough evaluation of the dam and fetuses has been performed because of loss of pregnancy. This evaluation should include metabolic screening of the dam for systemic disease, infectious disease evaluation, histopathology of expelled fetuses and placentae, and review of kennel/cattery husbandry including nutrition, medications and environmental factors. All results are normal or negative. Dams experiencing premature myometrial activity in one pregnancy may or may not exhibit it during subsequent pregnancies, but the syndrome can be a chronic cause of failure to reproduce.

In human medicine, preterm birth complicates 10–12% of human pregnancies, but it accounts for 80% of fetal morbidity and mortality. The diagnosis of preterm labor placing the fetus at risk of premature delivery is dependent upon evaluation of uterine contractility by tocodynamometry, and fetal fibronectin and transvaginal cervical length measurement determined via ultrasonography, which together have high negative predictive value. Amniocentesis is also advocated as a method of evaluating fetal lung maturation and microbial invasion of the amniotic cavity. The presence of contractions alone does not warrant intervention. Tocodynamometry identifies labor onset earlier than subjective maternal perceptions, and home uterine monitoring is advocated in high-risk groups as an initial screening test. Multifetal gestations (i.e., litters) are associated with exaggerated physiologic changes which promote premature labor and complicate tocolytic therapy. Women with histories of preterm deliveries do appear to be at risk for such in subsequent pregnancies.

If intervention is indicated, tocolytics agents have been commonly advocated. Antibiotics, bed and pelvic rest and hydration do not appear to have benefit. Contraindications to tocolytics therapy include severe preeclampsia, placental abruption, intrauterine infection, lethal congenital or chromosomal abnormalities, advanced cervical dilatation, and evidence of fetal compromise or placental insufficiency. Tocolytic agents inhibit myometrial contractions and include beta mimetics (terbutaline, ritodrine), magnesium sulfate, calcium channel blockers and prostaglandin synthetase inhibitors (indomethacin, ketorolac, sulindac). Contraindications to beta mimetics include maternal cardiac arrhythmias, poorly controlled diabetes mellitus and hyperthyroidism; fetal and maternal tachycardia and myocardial ischemia, maternal pulmonary edema and hypotension and fetal myocardial hypertrophy, hyperglycemia and hyperinsulinemia are potential side effects. A contraindication to magnesium sulfate
is maternal myasthenia gravis; side effects include maternal lethargy, muscle weakness, headache, pulmonary edema and cardiac arrest, and fetal respiratory depression, hypotonia, lethargy and demineralization. Contraindications to calcium channel blockers include maternal cardiac disease, renal disease and hypotension; side effects include maternal nausea, hypotension and headache. Contraindications to prostaglandin synthetase inhibitors include maternal renal or hepatic impairment; side effects include maternal nausea and gastroesophageal reflux disease, and fetal constriction of the ductus arteriosus, pulmonary hypertension, reversible renal impairment, intraventricular hemorrhage, hyperbilirubinemia and necrotizing enterocolitis. Physicians hope to intervene in the future with anticytokine (interleukin-10) and antiprostaglandin therapy to more completely suppress the pathogenic process at multiple sites along the pathway rather than just treating the processes at the end of preterm labor.

Small human trials based on prophylactic treatment with prostaglandin E2 inhibitors have been reported. Not all reported positive results with meta-analysis, the prevention of preterm delivery or the prevention of recurrent miscarriage appear to be based on the use of only the natural metabolite of progesterone, 17 alpha-hydroxyprogesterone caproate (17P). In one study, no increase in the rate of congenital anomalies in the progesterone group was noted over the control group. The benefit of 17P in preventing preterm delivery appears to be best in a cohort of women at very high risk, and the cohort still exhibited a high rate of preterm delivery (36%) despite significant reduction as compared to untreated control (54%), indicating that other causes of preterm delivery were at play. Tocolytic therapy was added in 17% of the treated group and 16% of the untreated control group. Interestingly, serum progesterone levels were not reported.

The maintenance of canine and feline pregnancy requires serum progesterone levels of > 1–2 ng/mL. Serum progesterone levels during pregnancy normally range from 15 to 90 ng/mL, declining gradually during the latter half of gestation and falling abruptly at term (usually the day before or the day of parturition). Progesterone promotes the development of endometrial glandular tissue, inhibits myometrial contractility (causes relaxation of myometrial smooth muscle), blocks the action of oxytocin, inhibits the formation of gap junctions, and inhibits leukocyte function in the uterus. In several species, local changes in the progesterone level or the ratio of progesterone to estrogen in the placenta, decidua or fetal membranes is important in the initiation of labor. Progesterone antagonists administered at term can result in an increased rate of spontaneous abortion. In the bitch, the corpora lutea are the sole source of progesterone, while in the queen, placental progesterone production occurs in the latter half of gestation. Canine luteal function is autonomous early in pregnancy but supported by luteotrophic hormones (LH and prolactin) after the second week of gestation.

Hypoluteoidism, primary luteal failure occurring before term gestation, is a potential but not yet documented cause of late-term abortion in otherwise normal bitches. It has been documented that the induction of abortion in a normal but undesired pregnancy requires a reduction of plasma progesterone levels < 2 ng/ml. The diagnosis of gestational loss caused by premature luteolysis is difficult, requiring documentation of inadequate plasma progesterone levels prior to abortion for which no other cause is found. Measurement of precise progesterone levels, especially in the critical 1–3 ng/ml range, is not accurate using currently available rapid in-house ELISA kits, necessitating the use of commercial laboratories in most practice situations. A few academic and human private laboratories provide more rapid (< 8 h) turnaround, facilitating the diagnosis.

Progesterone levels diminish in response to fetal death, thus documentation of a low progesterone level after an abortion does not establish the diagnosis of hypoluteoidism as the primary cause for reproductive failure. Administration of progesterone to maintain pregnancy in dams with primary fetal abnormalities, placentitis, or intrauterine infection can cause continued fetal growth with the possibility of dystocia and sepsis. Administration of excessive progesterone to maintain pregnancy in a dam not
actually requiring therapy can delay parturition and impact lactation, endangering the life of the bitch and her fetuses, and it can masculinize female fetuses.

Dams with documented low progesterone levels and historical late-term loss of pregnancy with no apparent pathology can also be evaluated for premature myometrial activity mid gestation, using uterine monitoring. Elaboration of prostaglandins from the endometrium and placenta associated with premature myometrial activity can result secondarily in luteolysis. Premature uterine activity endangering fetal survival can be identified before significant luteolysis occurs, and intervention indicated if the pregnancy is normal otherwise. Pharmacologic intervention to decrease myometrial activity is indicated, using progestational compounds and tocolytic agents alone or in combination.

Therapeutic intervention in primary hypoluteoidism can be accomplished with the administration of injectable natural progesterone or oral synthetic progestogens. Total serum levels of progesterone can be monitored only when supplemented with the natural product. Progesterone in oil is given intramuscularly at 2 mg/kg q 72 h. Altrengost (Regu-Mate, Hoechst-Roussel), a synthetic progestogen manufactured for use in the mare, is dosed orally at 0.088 mg/kg q 24 h. Both forms of supplementation must be discontinued in a timely fashion so as not to interfere with normal parturition, within 24 h of the due date with the oral synthetic product, and within 72 h with the natural, injectable depot form. This requires accurate identification of gestational length via prior ovulation timing (parturition expected to occur 64–66 days from the LH surge or initial rise in progesterone, or 56–58 days from the first day of cytologic diestrus). Less accurate identification of gestational length can be made from breeding dates (58–72 days from the first breeding), radiography, or ultrasound.

Terbutaline (Brethine, Ciba Geigy) 0.03 mg/kg PO q 8 h has been used to suppress uterine contractility in bitches and queens with historical loss of otherwise normal pregnancies preterm. The dose is ideally titrated to effect using tocodynamometry. Therapy is discontinued 24 h before term.

Further work evaluating the pathophysiology of premature labor and preterm delivery in the bitch and queen is needed, including evaluation of the ovary, placenta, myometrium and fetus for contributing factors. Multicenter studies including identification of the criteria for diagnosis of significant premature labor, specific therapy, outcome and followup (dam and neonatal health, subsequent pregnancies) is encouraged.

**Metabolic Conditions**

Gestational diabetes occurs infrequently in the bitch and queen and is attributed to the anti-insulin effect of progesterone (mediated by increased levels of growth hormone) during the luteal phase. Polydipsia, polyuria and polyphagia with weight loss occur. Higher protein, lower carbohydrate diets may be helpful in the queen, while high-fiber diets promote euglycemia in the bitch. Insulin may be indicated. Oversized fetuses can result from their increased production of insulin in response to maternal hyperglycemia, and may cause dystocia due to fetal-maternal mismatch.

Pregnancy toxemia in the bitch occurs as a result of altered carbohydrate metabolism in late gestation resulting in ketonuria without glycosuria or hyperglycemia. The most common cause is poor nutrition or anorexia during the last half of gestation. Hepatic lipidosis can occur. An improved plane of nutrition can resolve the condition in most cases, but termination of the pregnancy may be indicated in severe cases.

Puerperal tetany or eclampsia occurs most commonly during the first 4 weeks postpartum, but can occur in the last few weeks of gestation. The condition occurs in bitches more frequently than queens. Puerperal tetany can be life-threatening, caused by a depletion of ionized calcium in the extracellular compartment. Predisposing factors include improper perinatal nutrition, inappropriate calcium supplementation and heavy lactational demands. Small dams with large litters are at increased risk. Excessive prenatal calcium supplementation can lead to the development of puerperal tetany by
promoting parathyroid gland atrophy and inhibiting parathyroid hormone release, thus interfering with the normal physiologic mechanisms to mobilize adequate calcium stores and utilize dietary calcium sources. Thyrocalcitonin secretion is stimulated. The use of a balanced growth (puppy/kitten) formula commercial feed without additional vitamin or mineral supplementation is optimal during the second half of gestation and throughout lactation. Supplementation with cottage cheese should also be avoided, as it disrupts normal calcium-phosphorus-magnesium balance in the diet.

Metabolic conditions favoring protein binding of serum calcium can promote or exacerbate hypocalcemia, such as alkalosis resulting from prolonged hyperpnea during labor or dystocia. Hypoglycemia and hyperthermia can occur concurrently. Therapeutic intervention should be initiated immediately upon recognition of the clinical signs of tetany, without waiting for biochemical confirmation. The signs preceding the development of tonic-clonic muscle contractions (progressing to seizures) include behavioral changes, salivation, facial pruritus, stiffness/limb pain, ataxia, hyperthermia and tachycardia. Immediate therapeutic intervention should be instituted with a slow intravenous infusion of 10% calcium gluconate (1–20 ml) given to effect. Cardiac monitoring for bradycardia and arrhythmias should accompany administration; their occurrence warrants temporary discontinuation of the infusion and a slower subsequent rate. Because cerebral edema can occur from uncontrolled seizures, diazepam (1–5 mg intravenously) or barbiturates can be used to control persistent seizures once eucalcmia is attained. Mannitol may be indicated for cerebral inflammation and swelling. Corticosteroids are undesirable, because they promote calciuria, decrease intestinal calcium absorption and impair osteoclasia. Hypoglycemia should be corrected if present, and exogenous treatment for hyperthermia given if necessary. Once the immediate neurologic signs are controlled, a subcutaneous infusion of an equal volume of calcium gluconate - diluted 50% with saline - is given, repeated q 6–8 h until the dam is stable and able to take oral supplementation. Calcium gluconate or carbonate (10–30 mg/kg q 8 h) should be instituted. Each 500-mg calcium carbonate tablet (TUMS) supplies 200 mg calcium. Efforts to diminish lactational demands on the dam and improve her plane of nutrition are indicated. If response to therapy has been prompt, nursing can be gradually re instituted until the neonates can be safely weaned, usually at a slightly early age (3 weeks), and concurrent supplementation with commercial bitch/queen milk replacement is encouraged. The administration of calcium throughout lactation, but not gestation, may be attempted in dams with a history of recurrent eclampsia (calcium carbonate 500–4000 mg/dam/day divided).

**Infectious Disease**

**Canine Herpesvirus**

Adequate exposure of a nonimmune bitch to canine herpesvirus (CHV) during the last three weeks of gestation can result in infection of the dam and subsequently her neonates. Venereal transmission is believed to be rare and community (respiratory) transmission more common. Signs in the bitch are usually limited to a mild, clear upper respiratory discharge and soft sneezing. Late-term abortion or neonatal death within the first few weeks of life commonly results. The recently infected bitch generally has minimal clinical signs, but has inadequate time to form protective maternal antibodies and allow passive immunity (transplacental or transmammary) to be acquired by the neonates. Incompletely developed immune systems and inadequate thermoregulation during the first days of life make neonates vulnerable to systemic infection (bacterial and viral). Adequate ingestion of colostrum must occur promptly postpartum for puppies to acquire passive immunity. The transmission of protective immunity (placental or colostral antibodies) between a bitch and her puppies depends upon the prior existence of adequate serum maternal antibodies.
Transmission of CHV from an infected, viremic dam to neonates occurs subsequent to contact with infectious vaginal fluids or oronasal secretions. Signs in the neonate are progressive and severe and include anorexia (poor weight gain), dyspnea, abdominal pain, incoordination, diarrhea, serous to hemorrhagic nasal discharge and petechiation of the mucous membranes. The mortality rate in untreated litters infected in utero or during birth is commonly 100%, with deaths occurring during the first few days to 3 weeks of life. Infection in neonates born to a nonimmune bitch may also result from contact with CHV from another dog shedding the organism in the vicinity. Older naive (>3–4 weeks of age) puppies exposed to herpes virus may have an inapparent infection, but later central nervous signs including blindness and deafness have been observed. Subsequent litters of the bitch infected during a pregnancy are usually resistant to infection, having acquired circulating maternal antibodies.

Canine herpesvirus is a commonly blamed cause for fading puppy syndrome resulting in neonatal death. Premortem diagnosis of CHV infection in neonates can be challenging. Postmortem diagnostics include appropriate histopathology and virus isolation. Pathognomonic changes occurring in the kidneys include multifocal petechial hemorrhages, although this can be seen with bacterial septicemia and associated thromboembolic disorders as well. Intranuclear inclusion bodies can be difficult to find. Diagnosis by virus isolation or CHV-specific PCR is confirmatory and desirable, especially before litter mortality reaches 100%.

Until recently, treatment of CHV infection in neonates has been reported to be unrewarding and rare, with recovery suspected to be associated with residual cardiac and neurologic damage. Treatment with immune serum from affected dams is reported to be ineffective in infected puppies. Vaccine development is hampered by the poor immunogenicity of the herpes virus, as evidenced by other herpessviral vaccines developed for different species, such as feline and bovine rhinotracheitis. Successful treatment with the antiviral agent acyclovir has recently been reported.

Acyclovir is an antiviral agent with activity against a variety of viruses including herpes simplex. Acyclovir is preferentially taken up by susceptible viruses and converted into the active triphosphate form, inhibiting viral DNA replication. Acyclovir is poorly absorbed after oral administration and is primarily hepatically metabolized. Acyclovir can increase the toxicity of nephrotoxic drugs. The half-life in humans is approximately 3 hours. Its use in veterinary medicine is not well established, and it should be used with caution and only in situations where indicated. The safety and effectiveness in humans <2 weeks of age is not established. The dose was extrapolated from that for humans (20 mg/kg PO q 6 h x 7 days).

**Canine Brucellosis**

Brucellosis is the primary contagious infectious venereal disease of concern in canine reproduction. Canine brucellosis is caused by *B. canis*, a small, Gram-negative, non-spore-forming aerobic coccobacilli. *B. canis* was first isolated by Leland Carmichael in 1966. *Brucella abortus*, *B. melitensis* and *B. suis* have occasionally caused canine infections but are comparatively rare. Transmission occurs through direct exposure to bodily fluids containing an infectious dose of organism (semen, lochia, aborted fetuses/placentas, milk and urine). There are $2 \times 10^6$ colony-forming units in an infective dose. Transmission is therefore primarily oral, nasal, conjunctival and secondarily venereal (i.e., through the mucous membranes), the former associated with the ingestion or aerosolization of infectious materials. The aerosol route is especially important if kennel conditions are crowded. Transplacental transmission and direct cutaneous inoculation can occur.

Canine brucellosis has high morbidity but low mortality in the adult dog. The clinical systemic signs are often subtle (suboptimal athletic performance, lumbar pain, lameness, weight loss, lethargy). The primary clinical sign of canine brucellosis in the breeding bitch is pregnancy loss, which can occur early (day 20) in gestation, resulting in fetal resorption, or more commonly (75%) later in gestation (generally
45–59 days), resulting in abortion. Bitches with pregnancy loss early in gestation can appear to be infertile (failed to conceive) unless early ultrasonographic pregnancy evaluation is performed. Nongravid bitches can be asymptomatic or can show regional lymphadenopathy (pharyngeal if orally acquired, inguinal and pelvic if venereally acquired).

Infected dogs and bitches should be removed from breeding programs and quarantined. Eradication of the disease in kennel situations has not been successful without removal (culling) of all infected (current or historically) dogs. Because of the zoonotic potential of the disease and difficulty in actually eradicating the infection, euthanasia of affected dogs has been advised. Infection in household or small hobby kennel dogs often results in client requests for alternatives to euthanasia. Neutering decreases the amount of organism shed in semen and uterine discharge but does not eradicate the infection. Urine shedding can persist, and the organism can be found in internal organs and the bloodstream.

Antibiotic therapy has not been historically rewarding, likely due to the fact that the organism is intracellular and bacteremia periodic. Antibiotic therapy may reduce antibody titers without clearing the infection. Relapses are common. Combination therapy with tetracyclines (doxycycline or minocycline 25 mg/kg BID PO for 4 weeks) and dihydrostreptomycin (10–20 mg/kg BID IM or SC for 2 weeks, weeks 1 and 4) or an aminoglycoside (gentamicin 2.5 mg/kg BID IM or SC for 2 weeks, weeks 1 and 4) has been advocated as being the most successful, but unavailability, nephrotoxicity, parenteral therapy requirements, and expense remain problematic. Recently one study reported a slightly encouraging outcome of therapy with enrofloxacin (5.0 mg/kg BID PO for 4 weeks, often for multiple courses) in a small group of infected dogs and bitches. Enrofloxacin was not completely efficacious in eliminating B. canis, but it maintained fertility and avoided the recurrence of abortions, transmission of the disease to subsequently whelped puppies, and dissemination of microorganisms during parturition. Ultimately, however, most treated individuals remained culture positive.

Private breeders should require screening testing of all bitches presented for breeding and confirmatory negative testing if positive results occur during screening before accepting a bitch into their kennel. Stud dogs should be screened appropriately at least annually. Because of the potential for nonvenereal transmission, screening of maiden dogs and bitches before breeding is also recommended.

**Dystocia**

Although many bitches and queens deliver in the home or kennel/cattery setting without difficulty, requests for veterinary obstetrical assistance are becoming more common. The increased financial and emotional value of stud dogs, brood bitches, toms, queens and their offspring to the pet fancy makes the preventable loss of even one neonate undesirable. Breeding colonies in academic, scientific and industrial facilities need to maximize neonatal survival for financial and ethical reasons. Veterinary involvement in canine and feline obstetrics has several goals: to increase live births (minimizing stillbirths resulting from the difficulties in the birth process); to minimize morbidity and mortality in the dam; and to promote increased survival of neonates during the first week of life. Neonatal survival is directly related to the quality of labor. Optimal management of whelping/queening requires an understanding of normal labor and delivery in the bitch and queen, as well as the clinical ability to detect abnormalities in the birthing process.

Dystocia is defined as difficulty in the normal vaginal delivery of a neonate from the uterus. Dystocia must be diagnosed in a timely fashion for medical or surgical intervention to improve outcome. Additionally, the etiology of dystocia must be identified for the best therapeutic decisions to be made.
NORMAL PARTURITION

Gestation
Clinicians are commonly asked to ascertain if a bitch or queen is at term pregnancy, ready chronologically to deliver a litter, and then to intervene if labor has not begun. An accurate determination of gestational length can be difficult, especially if numerous copulations occurred and no ovulation timing was performed. Prolonged gestation is a form of dystocia. Gestation in the bitch is more challenging to calculate than in the cat, because bitches are spontaneous ovulators. Normal gestation in the bitch is 56 to 58 days from the first day of diestrus (detected by serial vaginal cytologies, defined as the first day that cytology returns to < 50% cornified/superficial cells), 64 to 66 days from the initial rise in progesterone from baseline (generally > 2 ng/ml), or 58 to 72 days from the first instance that the bitch permitted breeding. Predicting gestational length without prior ovulation timing is difficult because of the disparity between estrual behavior and the actual time of conception in the bitch, and the length of time semen can remain viable in the bitch reproductive tract (often up to > 7 days). Breeding dates and conception dates do not correlate closely enough to permit very accurate prediction of whelping dates. Additionally, clinical signs of term pregnancy are not specific: radiographic appearance of fetal skeletal mineralization varies at term; fetal size varies with breed and litter size; and the characteristic drop in body temperature (typically less than 99 degrees Fahrenheit) may not be detected in all bitches and varies in many. Breed, parity and litter size can also influence gestational length. Because the queen is an induced ovulator (ovulation follows coitus by 24–36 hours), gestational length can be predicted more accurately from breeding dates, assuming copulation provided adequate coital stimulation for the LH surge and subsequent ovulation, and a limited number of copulations were permitted. The gestational length of queens ranges from 52–74 days from the first to last breeding. The mean gestational length is 65–66 days. Because of the poor outcome with the delivery of premature puppies and kittens, elective intervention is best delayed until stage I labor has begun or prolonged gestation confirmed.

Labor and Delivery
Bitches typically enter stage I labor within 24 hours of a decline in serum progesterone to below 2–5 ng/mL, which occurs in conjunction with elevated circulating prostaglandins and is commonly associated with a transient drop in body temperature, usually to < 100 degrees Fahrenheit (33.7°C). Queens typically enter stage I labor 24 hours after serum progesterone levels fall to less than 2 ng/mL. Monitoring serial progesterone levels for impending labor is problematic due to the fact that in-house canine kits enabling rapid results are inherently less accurate between 2–5 ng/mL, and a rapid decline in progesterone levels can occur over a period of a few hours. Commercial laboratories offering quantitative progesterone by chemiluminescence typically have a 12- to 24-hour turnaround time, which is not rapid enough to enable decisions about an immediate indication for obstetrical intervention.

Stage I labor in the bitch normally lasts from 12 to 24 hours, during which time the uterus has myometrial contractions of increasing frequency and strength, associated with cervical dilatation. No abdominal effort (visible external contractions) is evident during stage I labor. Bitches may exhibit changes in disposition and behavior during stage I labor, becoming reclusive, restless, and nesting intermittently, often refusing to eat and sometimes vomiting. Panting and trembling may occur. Vaginal discharge is clear and watery.

Normal stage II labor in the bitch is defined to begin when external abdominal efforts can be seen, accompanying myometrial contractions to culminate in the delivery of a neonate. Presentation of the fetus at the cervix triggers the Ferguson reflex, promoting the release of endogenous oxytocin from the hypothalamus. Typically, these efforts should not last longer than 1–2 hours between puppies, although
great variation exists. The entire delivery can take between 1 and > 24 hours; however, normal labor is associated with shorter total delivery time and shorter intervals between neonatal births. Vaginal discharge can be clear, serous to hemorrhagic, or green (uteroverdin). Typically bitches continue to nest between deliveries, and may nurse and groom neonates intermittently. Anorexia, panting and trembling are common.

Stage III labor is defined as the delivery of the placenta. Bitches typically vacillate between stages II and III of labor until the delivery is complete. During normal labor, all fetuses and placentae are delivered vaginally, although they may not be delivered together in every instance.

The stages of labor in the queen can be similarly defined. Stage 1 labor in the queen is reported to last 4–24 hours and stages II and III from 2 to 72 hours, although completion of delivery of neonates within 24 hours is expected with normal queening.

Dystocia results from maternal factors (uterine inertia, pelvic canal anomalies, intrapartum compromise), fetal factors (oversize, malposition, malposture, anatomic anomalies), or a combination of both. For effective management, the recognition of dystocia must be made in a timely manner, and identification of etiologic factors made correctly.

Uterine inertia is the most common cause of dystocia. Primary uterine inertia results in the failure of delivery of any neonates at term and is thought to be multifactorial, including metabolic defects at the cellular level. An intrinsic failure to establish a functional, progressive level of myometrial contractility occurs. A genetic component may be present. Secondary uterine inertia results in the cessation of labor once initiated and consequential failure to deliver the entire litter. Secondary inertia can result from metabolic or anatomic (obstructive) causes, and is also thought to have a genetic component. Birth canal abnormalities such as vaginal strictures, stenosis from previous pelvic trauma or particular breed conformation, and intravaginal or intrauterine masses can cause obstructive dystocia. In most cases, canal abnormalities can be detected in the pre-breeding examination and can be resolved or avoided by elective cesarean section. Causes of intrapartum compromise rendering the dam unable to complete delivery include metabolic abnormalities such as hypocalcemia and hypoglycemia, systemic inflammatory reaction, sepsis, and hypotension (due to hemorrhage or shock).

Fetal factors contributing to dystocia most commonly involve mismatch of fetal and maternal size, fetal anomalies and fetal malposition and/or malposture. Prolonged gestation with small litter size can cause dystocia due to an oversize fetus(es). Fetal anomalies such as hydrocephalus and anasarca similarly can cause dystocia. Fetal malposition (ventrum of fetus proximal to the dam’s dorsum) and fetal malposture (flexed neck and scapulohumeral joints most commonly) promote dystocia as the fetus cannot transverse the birth canal smoothly.

An efficient diagnosis of dystocia is dependent upon taking an accurate history and performing a thorough physical examination in a timely manner. The clinician must quickly obtain a careful reproductive history detailing breeding dates, any ovulation timing performed, historical and recent labor, as well as a general medical history. The physical examination should address the general status of the patient, as well as include a digital and/or vaginoscopic pelvic exam for patency of the birth canal, evaluation of litter and fetal size (radiography most useful), assessment of fetal viability (Doppler or real-time ultrasound ideally) and uterine activity (tocodynamometry most useful).

A novel approach to veterinary obstetrical monitoring in use in the United States involves the use of external monitoring devices using tocodynamometry (Healthdyne Inc., Marietta, GA, USA) and a handheld Doppler (Sonicaid, Oxford Instruments, England) to detect and record uterine activity and fetal heart rates. These devices can be used either in the home setting or at the veterinary clinic. Their use requires that the hair coat be lightly clipped caudal to the ribcage, over the gravid area of the lateral flanks, to allow proper contact of the uterine sensor and fetal Doppler. The uterine sensor detects changes in intrauterine and intra-amniotic pressures. The sensor is strapped over the lightly clipped area
of the bitch’s/queen’s caudolateral abdomen using an elasticized strap. The sensor’s recorder is worn in a small backpack placed over the caudal shoulder area. Bitches/queens are at rest in the whelping/queening box or in a crate or cage during the monitoring sessions. The monitoring equipment is well tolerated. Subsequent to each recording session, data is transferred from the recorder via a modem using standard telephones. Fetal Doppler monitoring is performed bilaterally with a handheld unit with bitches/queens in lateral recumbency, using acoustic coupling gel. Directing the Doppler perpendicularly over a fetus results in a characteristic amplification of the fetal heart sounds, distinct from maternal arterial or cardiac sounds, which enables determination of fetal heart rates.

Interpretation of the contractile pattern in strips produced by the uterine monitor requires training and experience. Data is transferred by modem to obstetrical personnel capable of interpretation, who subsequently consult with the attending veterinary clinician and client. Recordings are made on a twice-daily, hour-long basis when home monitoring is performed, then intermittently on bitches or queens at home as indicated during active labor, or on site in the veterinary clinic for shorter periods of time (minimally 20 minutes) when patients are being evaluated for suspected dystocia.

The canine and feline uterus each has characteristic patterns of contractility, varying in frequency and strength before and during the different stages of labor.

Serial tocodynamometry in the bitch and queen permits evaluation of the progression of labor. During late term, the uterus may contract once or twice an hour before actual stage I labor is initiated. During stage I and II labor, uterine contractions vary in frequency from 0 to 12 per hour, and in strength from 15 to 40 mm Hg, with spikes up to 60 mm Hg. Contractions during active labor can last 2 to 5 minutes in duration. Recognizable patterns exist during prelabor and active (stages 1–3) labor. Aberrations in uterine contractility can be detected during monitoring. Abnormal, dysfunctional labor patterns can be weak or prolonged and often are associated with fetal distress. Additionally, the completion of labor (or lack thereof) can be evaluated via tocodynamometry.

**Figure 1.** Graph of uterine monitoring recordings, mm Hg vs. time in minutes. Normal baseline myometrial tracing, no contractions, prelabor. Variation off baseline at attachment of sensor (1–2 minutes).
Figure 2. Early active labor, stage II, uterine contractions and abdominal pushing
Caption: “C” = contraction

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Figure 3. Active labor, abdominal pushing with uterine inertia
Caption: Vertical spikes (c) indicate abdominal efforts.
Figure 4. Same bitch as in Figure 3, treated with 6 ml 10% calcium gluconate SC and 0.50 USP u oxytocin IM. Abdominal pushing evident in conjunction with uterine contractions ©. Puppy was delivered in 26 minutes.

Figure 5. Empty postpartum uterus
Figure 6. Uterine hyperstimulation, obstructed puppy, ecbolics contraindicated. Fetal distress was evident (persistent fetal bradycardia).

The presence of fetal distress is reflected by sustained deceleration of the heart rates. Normal canine and feline fetal heart rates at term are from 170 to 230 beats per minute (bpm), or at least 4 X the maternal heart rate. In the periparturient period, the cardiac output of the fetus/neonate is mainly dependent on heart rate as the right ventricle is relatively stiff (low compliance) and the autonomic nervous system is immature (minimal inotropic response to catecholamines). Decelerations associated with uterine contractions suggest mismatch in size between the fetus and dam, or fetal malposition or malposition. Transient accelerations occur with normal fetal movement. Fetal heart rates of ≤ 150 to 160 bpm indicate stress. Fetuses with heart rates ≤ 130 bpm have poor survival if not delivered within 2 to 3 hours, and fetuses with heart rates ≤ 100 bpm are an indication for immediate intervention to hasten delivery (medical or surgical) before their demise.

The use of uterine and fetal monitors allows the veterinary clinician to detect and monitor labor, as well as manage labor medically or surgically with insight instead of guesswork. At Guide Dogs for the Blind, Inc., the overall stillbirth rate declined from 9.2% to 2.5% with incorporation of uterine and fetal monitoring into the whelping process. Medical therapy for dystocia, based on the administration of oxytocin and calcium gluconate, can be directed and tailored based on the results of monitoring. Generally, the administration of oxytocin increases the frequency of uterine contractions, while the administration of calcium increases their strength. Oxytocin, 10 USP u/ml (American Pharmaceutical Partners, Inc., Los Angeles, CA, USA) is effective at mini doses, starting with 0.25 units SC or IM to a maximum dose of 4 units per bitch or queen. Higher doses of oxytocin or intravenous boluses can cause tetanic, ineffective uterine contractions that can further compromise fetal oxygen supply by placental compression. The frequency of oxytocin administration is dictated by the labor pattern, and it is generally not given more frequently than hourly. Calcium gluconate 10% solution with 0.465 mEq Ca++/ml (Fujisawa, Inc., USA) is given SC at 1 ml/5.5 kg BW as indicated by the strength of uterine contractions, generally no more frequently than every 4–6 hours. Calcium is given before oxytocin in most cases, improving contraction strength before increasing frequency. Additionally, the action of oxytocin appears to be improved when given 15 minutes subsequent to calcium. Most bitches/queens are eucalcemic, suggesting that the benefit of calcium administration is at a cellular or subcellular level.

Surgical intervention (cesarean section) is indicated if a bitch or queen fails to respond to medical management, or if fetal distress is evidenced despite adequate to increased uterine contractility (suggesting mismatch of maternal birth canal to fetal size, or fetal malposition or malposition.
incompatible with vaginal delivery), or if aberrant contractile patterns are noted by uterine monitoring. Well-orchestrated cesarean sections result when anesthetic and neonatal resuscitative protocols are established and coordinated, and the preoperative preparation of the dam optimized. It should always be remembered that the dam may be debilitated and require careful anesthetic management, there may be little time for routine preanesthetic preparation, and the dam may have been fed recently. Minimally, the hematocrit, total solids, serum calcium and glucose levels should be evaluated preoperatively. Intravenous fluid support at an operative rate minimally is indicated (10 ml/kg/h).

For premedication, atropine is best not given routinely, because it crosses the placenta and blocks the normal, adaptive bradycardic response of the fetus to hypoxia and causes relaxation of the lower esophageal sphincter, making maternal aspiration more likely. However, the use of an anticholinergic is indicated for the dam because of the anticipated vagal stimulation during manipulation of the gravid uterus. Glycopyrrolate (0.01–0.02 mg/kg SC) does not cross the placenta and is preferred. Most dams are tractable and do not need preanesthetic tranquilization, which has a depressant effect on the fetuses. Phenothiazine tranquilizers are transported rapidly across the placenta and are depressants. Alpha2-adrenoceptor agonists such as dexmedetomidine and xylazine are contraindicated because of their severe cardiorespiratory depressant effects. Similarly, the respiratory depressant effect of opioids makes them unpopular prior to removal of the fetuses. If tranquilization is necessary with an intractable dam, narcotic sedatives are preferable, as their effects can be reversed (naloxone 1–10 µg/kg IV or IM) during neonatal resuscitation. Metoclopramide (0.10–0.20 mg/kg) can be administered subcutaneously or intramuscularly prior to the induction of anesthesia to reduce the risk of vomiting during the procedure.

Preoxygenation by mask (5–10 minutes) is always indicated. Initial preparation of the abdomen (clipping and first scrubbing) can be undertaken during this time. For induction of anesthesia, dissociative agents such as ketamine and the barbiturates are best avoided, because they produce profound depression of the fetuses. Propofol (6 mg/kg IV to effect) appears to be most useful; because of its rapid redistribution, it therefore has a limited effect upon the fetuses after delivery. Mask induction actually produces more maternal and fetal hypoxemia than propofol induction. For maintenance of anesthesia, volatile agents are preferable, especially those with low partition coefficients such as isoflurane and sevoflurane. These agents show rapid uptake and elimination by the animal, and it may have a better cardiovascular margin of safety than the more soluble agents such as halothane. Nitrous oxide may be used to reduce the dose of other anesthetic agents; it is transferred rapidly across the placenta and, although it has minimal effects upon the fetus in utero, it may result in a significant diffusion hypoxia after delivery. Using a local anesthetic (bupivacaine 2 mg/kg) line block in the skin and subcutaneous tissues prior to incising permits a more rapid entry to the abdomen while the dam is making transition from propofol induction to inhalant maintenance, and it helps with postoperative discomfort.

Operative speed is important, because surgical delay and prolonged anesthetic time are associated with fetal asphyxia and depression. However, care should be taken during incision of the linea alba to ensure that the gravid uterus is not also incised. Ideally, the uterus should be exteriorized and packed off with moistened laparotomy sponges to prevent abdominal contamination with uterine fluid. This process should be undertaken carefully to ensure that the uterus and its broad ligament do not tear; it may be easier in some cases to exteriorize one horn at a time. The uterus should be penetrated in a relatively avascular area, and it is best to elevate the uterine wall from the fetus and to extend the incision with scissors to ensure that the fetus is not lacerated. The fetuses may be brought to the incision by gently ‘milking’ them along the uterus, although in some cases or in large dams, it may be necessary to make more than one incision. As the fetal fluid is released, it is best to remove this by suction and then to clamp the umbilicus (twice, incising between clamps) before passing the fetus to an
assistant for immediate resuscitation. After each fetus is removed, the associated placenta should be detached by gentle traction, but the placentas may be left in situ if they are firmly attached and their removal causes significant hemorrhage. Placentas can be spontaneously passed postoperatively or managed medically. It is essential that the uterine horns, the uterine body and the vagina are inspected thoroughly to ensure that all fetuses have been removed. Finally, after closure the uterus, its broad ligament and the vascular supply should be inspected carefully to ensure that any previously unnoticed tears have been identified before closure of the abdomen. Ovariohysterectomy at the time of cesarean section is again the option of the surgeon and owner, but it results in longer anesthetic time for the dam, delayed nursing for the neonates, and increased loss of blood in the dam, so it should be postponed if reasonable. There is some belief that estrogen acts in a permissive fashion for prolactin receptors in the mammary glands, making ovary removal at cesarean section undesirable. If uterine viability is questionable, an ovariohysterectomy should be performed. In the normal dam, the uterus will begin to involute shortly after removal of the fetuses, but if this is not the case, oxytocin may be administered (0.25–1.0 u per dam) to facilitate involution and arrest any hemorrhage; this also promotes milk letdown.

Postsurgical discomfort should be acknowledged in the dam. Once the fetuses are removed, narcotic analgesia can be administered parenterally to the dam. Postoperatively, nonsteroidal antiinflammatoratories are not advisable due to their uncertain metabolism by the nursing neonates with immature renal and hepatic metabolism. Narcotic analgesia is preferable. Oral narcotics such as tramadol, 10 mg/kg/day in divided doses, provide excellent postoperative analgesia for nursing bitches with minimal sedation of the neonates. In all cases, clients should be advised to closely monitor bitches postoperatively until normal maternal behavior emerges. Post cesarean section, bitches can be clumsy and inattentive to the neonates and can even become aggressive, as the normal mechanisms of maternal bonding have been bypassed. Nursing should be supervised and neonatal care ensured.

**Immediate Postpartum Period**

Normally, dams stay very close to their offspring during the first 2 weeks postpartum, leaving the whelping/queening box briefly, if at all, to eat and eliminate. They are alert and content to remain with their offspring. Some protective dams may show aggression to housemate animals or even people with whom they are normally tolerant; such behavior tends to dissipate after 1–2 weeks of lactation. Lactation typically presents the greatest nutritional and caloric demand of the female’s life. Weight loss and dehydration may occur and impact lactation if food and water are not made readily available; sometimes this entails leaving both in the nest box with a nervous dam. Partial anorexia can be exhibited during the last weeks of gestation and in the immediate postpartum period, but the appetite should return and increase as lactation progresses. Poor appetite during the last weeks of gestation can be due to displacement of the gastrointestinal tract by the gravid uterus. Partial anorexia early in the postpartum period can occur secondary to digestive upset following the consumption of numerous placentae. Diarrhea can occur secondary to increased rations and rich food (bacterial overgrowth secondary to carbohydrate malassimilation). Marked postpartum effluvium is normal in the bitch, usually occurring at 4–6 weeks after whelping, and sparing only the head. This is usually more marked than that which occurs in conjunction with the typical estrous cycle, and can be interpreted as pathologic by an owner, especially in conjunction with the weight loss typically associated with lactation.

The body temperature of the dam may be mildly elevated (<103.0 degrees F) in the immediate postpartum period, reflecting anticipated normal inflammation associated with parturition, but it should return to normal levels within 24–48 hours. If a cesarean section took place, differentiating normal postsurgical inflammation from fever associated with pathology may be difficult. The physical examination and a complete hemogram help the clinician differentiate between the two. Normal
postpartum lochia is brick-red in color, nonodorous, and diminishes over several days to weeks (uterine involution and repair occur for up to 16 weeks in the bitch). The mammary glands should not be painful; rather they are symmetric and moderately firm without heat, erythema, or palpable firm masses. If expressed, normal milk is grey to white in color and of watery consistency.

**CLINICAL PROBLEMS**

**Inappropriate Maternal Behavior**

Appropriate maternal behavior is critical to neonatal survival and includes attentiveness, facilitation of nursing, retrieving neonates, grooming and protecting neonates. Although maternal behavior is instinctual, it can be negatively influenced by anesthetic drugs, pain, stress, and excessive human interference. Maternal bonding is a pheromone-mediated event initiated at parturition. Whelping and queening should take place in quiet, familial surroundings, with minimal human interference, yet adequate supervision. Dams with good maternal instincts exhibit caution when entering or moving about the nest box so as not to traumatize neonates by stepping or lying on them. A guardrail along the inside of the whelping box prevents inadvertent smothering of canine neonates.

The neuroendocrine reflex regulating mammary gland myoepithelial cell contraction and subsequent milk ejection is mediated by oxytocin and activated by neonatal suckling. During stress, epinephrine induces vasoconstriction, blocking the entry of oxytocin into the mammary gland and preventing milk ejection. A nervous, agitated dam will likely have poor milk availability. Dopamine antagonist tranquilizers, with minimal prolactin interference (acepromazine 0.01–0.02 mg/kg) administered at the lowest effective dose to minimize neonatal sedation, can improve maternal behavior and mild ejection in nervous dams. Piling of littermates near their dam facilitates the maintenance of their adequate body temperature (neonates cannot thermoregulate/shiver for up to 4 weeks of age) and makes nursing readily available. Normal maternal behavior includes gentle retrieval of neonates who have become dispersed and isolated across the nest box. Grooming of the neonates immediately following parturition stimulates their cardiovascular and pulmonary function and removes amniotic fluids. Dams demonstrating little interest in resuscitating neonates can have poor maternal behavior throughout the postnatal period. Later, maternal grooming stimulates reflex neonatal urination and defecation and maintains the neonatal coat in a clean, dry state. Occasionally, excessive protective behavior or fear-induced maternal aggression can occur. Mild tranquilization of the dam with an anti-anxiety agent can help, but neonatal drug administration via the milk can be problematic. Benzodiazepines, GABA synergists, are reportedly superior to phenothiazines for fear-induced aggression (diazepam 0.55–2.2 mg/kg). The role of newer anti-anxiety pharmaceuticals in maternal aggression has not been described in a controlled setting.

**Uterine Disorders**

Complete or partial prolapse of the uterus is an uncommon postpartum condition in the bitch, occurring rarely in the queen. The diagnosis is based on palpation of a firm, tubular mass protruding from the vulva postpartum and inability to identify the uterus with abdominal ultrasonography. Vaginal hyperplasia and prolapse, secondary to a hypersensitivity of focal (periurethral) vaginal mucosa to estrogen, can recur near parturition and should be ruled out by physical examination, vaginoscopy, or contrast radiography. The prolapsed uterine tissues are at risk for maceration and infection from exposure and contamination. The size of most bitches and queens precludes manual replacement; laparotomy and ovariohysterectomy are usually indicated.

Rupture of the uterus occurs most commonly with very large litters causing marked stretching and thinning of the uterine wall, especially in multiparous dams with dystocia. Immediate laparotomy for retrieval of fetuses and repair or removal of the uterus, as well as culture and lavage of the abdominal
cavity, is indicated. The uterus should be carefully examined at any cesarean section for any areas with or prone to rupture. Peritonitis can result from an undetected uterine tear. A unilateral hysterectomy can be considered if the damaged area is limited and the dam is valuable to a breeding program.

The persistence of serosanguineous to hemorrhagic vaginal discharge beyond 16 weeks postpartum can indicate subinvolution of the placental sites of attachment (SIPS) in the bitch. Histologically, fetal trophoblastic cells have persisted in the myometrium instead of degenerating, endometrial vessel thrombosis is lacking, and normal involution of the uterus is prevented. Normal interplacental regions exist. Eosinophilic masses of collagen and dilated endometrial glands protrude into the uterine lumen, oozing blood. The cause is unknown, blood loss is usually minimal, intrauterine infection not present, and fertility is unaffected. Treatment is generally not necessary, as recovery is spontaneous and symptoms mild. In the uncommon situation where vaginal bleeding from SIPS is copious enough to cause serious anemia, coagulopathies (likely defects in the intrinsic pathway or thrombocytopenia/thrombocytopenias), trauma, neoplasia of the genitourinary tract, metritis and proestrus should be ruled out. Vaginal cytology, vaginoscopy, coagulation testing and abdominal ultrasound assist in the diagnosis. Treatment in these cases can be attempted with ergonovine (0.2 mg/15 kg IM) administered once or twice. The benefit of therapeutic prostaglandins and/or oxytocin is questionable and not proven in any controlled study. The preventative value of oxytocin given in the immediate postpartum period is also unproven. Laparotomy and ovariohysterectomy are curative. Histologic examination of the uterus is indicated to confirm the diagnosis.

Acute infection of the postpartum endometrium should be suspected if lethargy, anorexia, decreased lactation and poor mothering occur accompanied by fever and malodorous vaginal discharge. Metritis is serious and sometimes preceded by dystocia, contaminated obstetrical manipulations, or retained fetuses and/or placentae. Hematologic and biochemical changes often suggest septicemia, systemic inflammation reaction and endotoxemia. Vaginal cytology shows a hemorrhagic to purulent septic discharge. Ultrasound of the abdomen allows evaluation of intrauterine contents and the uterine wall. Retained fetuses and placentae can also be identified with ultrasound. A guarded cranial vaginal culture is likely representative of intrauterine flora and should be submitted for both aerobic and anaerobic culture and sensitivities, and it permits retrospective assessment of empirically selected antibiotic therapy. Bacterial ascension from the lower genitourinary tract is more common than hematogenous spread, and *Escherichia coli* is the most common causative organism in both bitches and queens. Therapy consists of intravenous fluid and electrolyte support, appropriate bactericidal antibiotic administration and pharmacologic uterine evacuation, usually with prostaglandin F2 alpha (in the United States) at a dose of 0.10–0.20 mg/kg q 12–24 h for 3–5 days. An ovariohysterectomy may be indicated if the bitch’s condition permits, and she is poorly responsive to medical management. Ergonovine (0.2 mg/15 kg given once IM) is also an effective ecballotic agent, but it may cause rupture of a friable uterine wall. Synthetic prostaglandins offer more uterine-specific therapy where available. Oxytocin is unlikely to promote effective uterine evacuation when administered > 24–48 hours postpartum. Nurslings should be hand-reared if the dam is seriously sick. Metritis can become chronic and cause infertility.

**Mammary Disorders**

Agalactia is defined as a failure to provide milk to neonates. Primary agalactia, a lack of mammary development during gestation, results from a failure of milk production and is uncommon. A defect in the pituitary ovarian mammary gland axis is suspected. The use of progesterone compounds late in gestation can interfere with lactation. Secondary agalactia, a lack of milk availability due to a failure of ejection, is more common. Mammary development is marked, but milk cannot be readily expressed through the teat sphincter. The normal production of colostrum in the immediate postpartum period should not be confused with agalactia. Agalactia can occur secondary to premature parturition, severe
stress, malnutrition, debility, metritis, or mastitis. Treatment includes providing supplementation to the neonates while encouraging suckling to promote milk ejection, providing optimal levels of nutrition and adequate water to the dam, and resolution of any underlying disease. If detected early, milk letdown can often be induced pharmacologically. Mini dose oxytocin, 0.25–1.0 units per injection, is given subcutaneously every 2 hours. Neonates are removed for 30 minutes post injection and then encouraged to suckle, or gentle stripping of the glands is performed. Metoclopramide, 0.1–0.2 mg/kg SC is given q 12 h (dopamine antagonist) to promote milk production. Therapy is usually rewarding within 24 hours. Some authors advise a much higher dose of metoclopramide, but neurologic side effects become possible.

Galactostasis can cause engorgement and edema of the mammary gland with associated discomfort, making further nursing unlikely, and becoming self-perpetuating. Galactostasis occurs secondary to inverted or imperforate teats, failure to rotate nurslings, litter loss, an unusually small litter, or rarely with pseudocyesis.

Mastitis, septic inflammation of the mammary gland, can be acute and fulminate or chronic and low grade, involving a single or multiple mammary glands. Coliforms, staphylococci, and streptococci are most commonly isolated in both bitches and queens. The source of bacteria is cutaneous, exogenous or hematogenous. Mild mammary discomfort and heat, galactostasis, cutaneous inflammation, and the presence of an intramammary mass are the earliest signs. Milk is commonly discolored red or brown due to the presence of red and white blood cells. Moderate cases exhibit pain, reluctance to nurse or lie down, anorexia and lethargy. Fever can be marked and may precede other clinical signs. Advanced cases can present in septic shock, with abscessed or necrotic glands. The diagnosis is based upon physical examination. Milk cell counts in bitches are not predictive of mastitis. Culture and sensitivity of milk collected aseptically from affected glands allows retrospective evaluation of antibiotic selection. Therapy should begin immediately, consisting of broad-spectrum, bactericidal antimicrobials and gentle physical therapy. Analgesics may be indicated; neonates tolerate opioid analgesia in the dam. First-generation cephalosporins (cephalexin 10–20 mg/kg q 8–12 h) and beta lactamase-resistant penicillins (Clavamox 14 mg/kg q 12 h) are advised and safe for the neonates. Antibiotic therapy may be warranted until weaning and can preclude further nursing if sensitivities force the choice of a drug potentially toxic to neonates. Warm compresses or whirlpool therapy of the affected gland with gentle stripping of milk can potentially avert abscessation and rupture of the gland. Severe necrosis warrants mastectomy (when the dam is stabilized) and aggressive wound management. Anti-prolactin therapy (cabergoline 1.5–5.0 µg/kg/day divided BID) may be indicated in severe cases to reduce lactation. There is no evidence that nursing from affected glands is problematic for neonates, but they tend to avoid glands which are difficult to obtain milk from. The affected gland should be protected from trauma from nest box edges and neonatal claws. Mastitis can recur in subsequent lactations regardless of preventative measures taken. Early detection and treatment are optimal, rather than prophylactic antibiotics, which tend to favor resistant organisms.

ENDNOTE
a. VPI - Veterinary Perinatal Specialties, Inc., 9111 W. 38th Ave., Wheat Ridge, CO 80033, USA; (303) 423 3429; Fax: (303) 423 8242; email wlpwise@aol.com
Canine and Feline Neonatal Resuscitation: Techniques to Improve Outcome
Autumn P. Davidson, DVM, MS, BS, DACVIM
University of California, Davis, CA, USA
Average reported neonatal mortality rates (greatest during the first week of life) vary, ranging from 9–26%. Prudent veterinary intervention in the prenatal, parturient and postpartum periods can increase neonatal survival by controlling or eliminating factors contributing to puppy morbidity and mortality. Poor prepartum condition of the dam, dystocia, congenital malformations, genetic defects, injury, environmental exposure, malnutrition, parasitism and infectious disease all contribute to neonatal morbidity and mortality. Optimal husbandry impacts neonatal survival favorably by managing labor and delivery to reduce stillbirths, controlling parasitism and reducing infectious disease, preventing injury and environmental exposure, and optimizing nutrition of the dam and neonates. Proper genetic screening for selection of breeders minimizes inherited congenital defects. The neonatal period can be divided into the prepartum (prenatal) period, parturition, and the postpartum neonatal period; we will focus on the latter here.

Optimal neonatal resuscitation following birth (if the dam fails to do so) or caesarean section involves the same “A-B-Cs” as any cardiopulmonary resuscitation. First, prompt clearing of airways (“A”) by gentle suction with a bulb syringe; drying and stimulation of the neonate to promote respiration (“B”); and avoiding of chilling are performed. Neonates should not be swung to clear airways, as described in the veterinary literature, because of the potential for cerebral hemorrhage from concussion. The use of doxapram as a respiratory stimulant is unlikely to improve hypoxemia associated with hypoventilation, and it is not recommended. Spontaneous breathing and vocalization at birth are positively associated with survival through 7 days of age. Intervention for resuscitation of neonates following vaginal delivery should take place if the dam’s actions fail to stimulate respiration, vocalization, and movement within one minute of birth.

Cardiopulmonary resuscitation for neonates who fail to breathe spontaneously is challenging, yet potentially rewarding. Ventilatory support should include constant-flow \( O_2 \) delivery by facemask. If this is ineffective after one minute, positive pressure with a snugly fitting mask or endotracheal intubation and rebreathing bag (using a 2-mm endotracheal tube or a 12- to 16-gauge intravenous catheter) is advised. Anecdotal success with Jen Chung acupuncture point stimulation has been claimed when a 25-gauge needle is inserted into the nasal philtrum at the base of the nares and rotated when bone is contacted. Cardiac stimulation (“C”) should follow ventilation support, as myocardial hypoxemia is the most common cause of bradycardia or asystole. Direct transthoracic cardiac compressions are advised as the first step; epinephrine is the drug of choice for cardiac arrest/standstill (0.2 mg/kg administered best by the intravenous or intraosseous route). Venous access in the neonate is challenging; the single umbilical vein is one possibility. The proximal humerus, proximal femur and proximo-medial tibia offer intraosseous sites for drug administration. Atropine is currently not advised in neonatal resuscitation. The mechanism of bradycardia is hypoxemia-induced myocardial depression rather than vagal mediation, and anticholinergic-induced tachycardia can actually exacerbate myocardial oxygen deficits.

**BEYOND THE ABCS**
Chilled neonates can fail to respond to resuscitation. Loss of body temperature occurs rapidly when a neonate is damp. Keeping the neonate warm is important during resuscitation and in the immediate postpartum period. During resuscitation, placing the chilled neonate’s trunk into a warm-water bath
(95–99°F) can improve response. Working under a heat lamp or within a Bair hugger warming device is helpful. Post resuscitation, neonates should be placed in a warm box (a Styrofoam picnic box with ventilation holes is ideal) with warm bedding until they can be left with their dam.

Neonates lack glucose reserves and have minimal capacity for gluconeogenesis. Providing energy during prolonged resuscitation efforts becomes critical. Clinical hypoglycemia involves blood glucose levels less than 30 to 40 mg/dl, and it can be treated with dextrose solution intravenously/intraosseously, at a dose of 0.5 to 1.0 g/kg using a 5% to 10% solution, or a dose of 2 to 4 ml/kg of a 10% dextrose solution. Single administration of parenteral glucose is adequate if the puppy can then be fed or nurses. Fifty percent dextrose solution should only be applied to the mucous membranes because of the potential for phlebitis if administered intravenously; however, circulation must be adequate for absorption from the mucosa. Neonates administered dextrose should be monitored for hyperglycemia because of immature metabolic regulatory mechanisms. If a neonate is too weak to nurse or suckle, a mixture of a warmed, balanced crystalloid (lactated Ringer’s solution or Normosol solution) and 5% dextrose may be administered subcutaneously at a dose of 1 ml per 30 g of bodyweight, until the pup can be fed or nurses. A balanced, warmed nutrient-electrolyte solution can be administered orally by stomach tube every 15–30 minutes until the neonate is capable of suckling.

**When to Stop Resuscitation**
- No response after 15–20 minutes of effort (continued agonal respiration, bradycardia)
- Serious congenital defect detected (cleft palate, loud murmur, gastroschisis, large omphalocele, large fontanel)

**Husbandry: The First Days**
Post resuscitation or within the first 24 hours of a natural delivery, a complete physical examination should be performed by a veterinarian, technician, or knowledgeable breeder. The oral cavity, hair coat, limbs, umbilicus and urogenital structures should be visually inspected. The mucous membranes should be pink and moist, a suckle reflex present, the coat full and clean, the urethra and anus patent. A normal umbilicus is dry without surrounding erythema. The thorax should be ausculted; vesicular breath sounds and a lack of murmur are normal. The abdomen should be pliant and not painful. A normal neonate will squirm and vocalize when examined, nurse and sleep quietly when returned to the dam. Normal neonates will attempt to right themselves and orient by rooting toward their dam. Neonates are highly susceptible to environmental stress, infection, and malnutrition. Proper husbandry is critical and should include daily examination of each neonate for vigor and recording of weight.

**Warmth**
Puppies lack thermoregulatory mechanisms until four weeks of age; thus, the ambient temperature must be high enough to facilitate maintenance of a body temperature of at least 97°F (36°C). Hypothermia negatively impacts immunity, nursing, and digestion. Exogenous heat should be supplied, best in the form of an overhead heat lamp. Heating pads run the risk of burning neonates incapable of moving away from excessively hot surfaces.

**Neonatal normal body temperature (rectal)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>95–99°F</td>
</tr>
<tr>
<td>Week 2–3</td>
<td>97–100°F</td>
</tr>
<tr>
<td>At weaning</td>
<td>99–101°F</td>
</tr>
</tbody>
</table>
Environmental warmth required

<table>
<thead>
<tr>
<th>Week</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>84–89°F</td>
</tr>
<tr>
<td>Weeks 2/3</td>
<td>80°F</td>
</tr>
<tr>
<td>Week 4</td>
<td>69–75°F</td>
</tr>
<tr>
<td>Week 5</td>
<td>69°F</td>
</tr>
</tbody>
</table>

Chilled neonates must be rewarmed slowly (30 minutes) to avoid peripheral vasodilation and dehydration. Tube feeding should be delayed until the neonate is euthermic; hypothermia induces ileus, and regurgitation and aspiration can result.

Immunity

Incomplete immunity systems during the first 10 days of life make neonates vulnerable to systemic infection (most commonly bacterial and viral). Adequate ingestion of colostrum must occur promptly postpartum for puppies to acquire passive immunity. The intestinal absorption of IgG generally ceases by 24 hours after parturition. Colostrum-deprived kittens given adult cat serum at a dose of 150 ml/kg SC or IP developed serum IgG levels comparable with suckling littermates; however, colostrum-deprived puppies given 40 ml/kg adult dog serum orally and parenterally failed to match sucking littermates’ IgG levels. Neonates should be encouraged to suckle promptly after resuscitation is completed; this usually necessitates close monitoring after a caesarean section, as the dam is still groggy from anesthesia. Replacement serum or plasma can be given orally within the first 24 h of life or parenterally (SC or IP) after 24 h of life at a dose of 0.10 ml/gm body weight. Maternal instincts (protecting, retrieving, grooming, nursing) usually return within 24 hours.

The umbilicus of neonates should be treated with tincture of iodine immediately after birth to reduce contamination and prevent ascent of bacteria into the peritoneal cavity (omphalitis-peritonitis).

Neonatal bacterial septicemia can cause rapid deterioration, resulting in death if not recognized and treated promptly. Factors that reportedly predispose a puppy to septicemia include endometritis in the bitch, a prolonged delivery/dystocia, feeding of replacement formulas, the use of ampicillin, stress, low birthweight (< 350 g for a medium-size breed), and chilling with body temperature < 96°. The organisms most frequently associated with septicemia are *E. coli*, streptococci, staphylococci, and *Klebsiella* spp. Premortem diagnosis can be challenging; clinical signs may not be noted due to sudden death. Commonly, a decrease in weight gain, failure to suckle, hematuria, persistent diarrhea, unusual vocalization, abdominal distension and pain, and sloughing of the extremities indicate septicaemia may be present. Prompt therapy with broad-spectrum, bactericidal antibiotics; improved nutrition via supported nursing, tube feeding, or bottle feeding; maintenance of body temperature; and appropriate fluid replacement are indicated. The third-generation cephalosporin antibiotic, ceftiofur sodium (Naxcel; Pharmacia and Upjohn), is an appropriate choice for neonatal septicemia, as it alters normal intestinal flora minimally and is usually effective against the causative organisms. Ceftiofur sodium should be administered at a dose of 2.5 mg/kg SC q 12 h for no longer than 5 days. Because puppies less than 48 hours old have reduced thrombin levels, presumptive therapy with vitamin K1 may be used (0.01–1.0 mg SC per puppy).

Groceries

Neonates have minimal body fat reserves and limited metabolic capacity to generate glucose from precursors. Glycogen stores are depleted shortly after birth, making adequate nourishment from nursing vital. Even minimal fasting can result in hypoglycemia. Hypoglycemia can also result from endotoxemia, septicemia, portosystemic shunts, and glycogen storage abnormalities. Oral fluid and glucose
replacement may be preferable if the puppy has an adequate swallowing reflex and is not clinically compromised. The neonatal caloric requirement is 133 calories/kg/day during the first week of life, 155 calories/kg/day for the second, 175–198 calories/kg/day for the third, and 220 calories/kg/day for the fourth. Commercially manufactured milk replacement formulas (Esbilac - Pet-Ag Inc., Elgin, IL; Puppy Milk Replacer Formula: Eukanuba, The Iams Co., Dayton, OH; Veta-Lac Powder for Puppies: Vet-A-Mix, Shenandoah, IA, KMR- Pet-Ag Inc., Elgin, IL) are usually superior to homemade versions. The use of milk obtained from the dam can be considered, if available. An osmotic diarrhea (usually yellow, curdled stool appearance) can result from overfeeding formula, necessitating diluting the product 50% with water or a balanced crystalloid such as lactated Ringer’s solution. Neonates should gain weight steadily from the day after birth (a transient mild loss from birthweight is acceptable on day 1); puppies gaining 1–3 grams per day per pound (2.2 kg) of anticipated adult weight, and kittens 50–100 grams weekly. Neonatal weights should be recorded daily for the first two weeks, then every 3 days until a month of age. Healthy, well-nourished neonates are quiet and sleep when not nursing.

**Normal Neonatal Weight Gain**
Increase of 5–10% bodyweight per day

**Table 1. Neonatal resuscitation kit**
- Syringes (tb), acupuncture needles or 28 G needles
- Epinephrine freshly diluted to 1:1000, 50% dextrose freshly diluted to 2.5–5%
- Oxygen sources
- Suction (pediatric bulb syringes, Dee aspirators)
- Small face masks
- Towels (smallish and lots of them)
- Heat source (Baer, warm-water blanket, infrared lamp)
- Puppy box (Styrofoam) with heat support
- Multiple clean mosquito forceps and small scissors
- 3-0 gut suture for umbilical cords needle removed, cut in 5” lengths
- Tincture of iodine
- Bowls for warm-water baths
- Pediatric/neonatal stethoscope
- Doppler
- Neonatal scale

**Neonatal Resuscitation Drugs**
- Dilute epinephrine
- Dilute dextrose
- Ceftriaxone
- Vitamin K1
- Narcotic reversal
**Tips and Tricks for Corneal Ulcers, Recurrent or Complex in Our Canine Patients**
Chantale L. Pinard, DVM, MSc, DACVO

This practical conference will present a brief overview of the pathophysiology of corneal ulcers. The differences between simple, recurrent and complex ulcers will be discussed, as well as the value of different diagnostic tests. Cases of canine corneal ulcers will be used as examples to present therapeutic options available to veterinary practitioners.

**Pathophysiology of the Cornea**
Corneal ulceration occurs commonly from trauma, chronic irritation, and/or a high corneal fragility due to a nutritional or immune deficiency (i.e., KCS, diabetes mellitus...). The epithelium (the protective layer of the cornea) erodes, and the exposure of the stromal layer takes place. The corneal stroma has no defense mechanism (blood, lymph vessels) and therefore is at the mercy of the corneal microenvironment. During ‘normal’ conditions, the lacrimal immune factors fight bacteria while the epithelium is migrating to cover the denuded stroma.

**Chronology of Corneal Healing**
It is important to remember the sequence of events when the cornea is ulcerated, because at each step, one or more complications may alter this timeline and lead to adverse or unexpected results.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Normal event</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 hour</td>
<td>Migration of the epithelial cells located at the edge of ulcer</td>
<td>- Chronic irritation prevents the migration of epithelial cells (friction from the eyelids)</td>
</tr>
<tr>
<td>24–72 hours</td>
<td>Covering of the corneal stroma by a layer of epithelial cells</td>
<td>- Chronic irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fragility of epithelial cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Infection and release of toxic factors (collagenases, protease)</td>
</tr>
<tr>
<td>4 days +</td>
<td>Appearance of corneal limbal blood vessels</td>
<td>Application of antiinflammatory solutions (nonsteroidal or corticosteroids)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prevents the formation (or causes delays in migration) of corneal vessels</td>
</tr>
<tr>
<td>~ 7 days</td>
<td>The epithelial layer is restored</td>
<td>- Chronic irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fragility of epithelial cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Infection and release of toxic factors (collagenases, protease)</td>
</tr>
<tr>
<td>30 days</td>
<td>Anchoring of desmosomes and hemidesmosomes of epithelial cells to stromal layer</td>
<td>Ulcer recurrent secondary to corneal sequestrum (hyaline layer on the exposed face of the stroma)</td>
</tr>
</tbody>
</table>
## Definitions of Corneal Ulcers
The classification of corneal ulcers is important, as it will direct the veterinarian toward a plan of action. Here are some criteria that can help to classify corneal ulcers.

<table>
<thead>
<tr>
<th>Simple ulcer</th>
<th>Recurrent ulcer</th>
<th>Complex ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth</td>
<td>Superficial&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Superficial&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infection</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sequestrum</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Diagnostics tests</td>
<td>No</td>
<td>Corneal debridement under topical anesthesia</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Bacteriostatic</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>No</td>
<td>Corneal debridement with linear keratotomy</td>
</tr>
<tr>
<td>Fluorescein negative&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2–3 days</td>
<td>7–14 days</td>
</tr>
</tbody>
</table>

<sup>a</sup> Less than 1/3 of the stromal layer
<sup>b</sup> In a “normal” environment

## Clinical Presentation
Several clinical signs may be noted once a cornea is ulcerated. These clinical signs depend on the cause, severity and chronicity of the corneal ulcer. The application of topical anesthetic can help control the ocular pain and therefore facilitate the examination of the affected eye; by instilling one drop of topical anesthetic, blepharospasm decreases significantly and the third eyelid retracts.

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Simple ulcer</th>
<th>Recurrent ulcer</th>
<th>Complex ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular pain</td>
<td>Ocular pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ocular pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pain due to uveitis</td>
</tr>
<tr>
<td>Ocular discharge</td>
<td>Serous</td>
<td>Serous</td>
<td>Serous to mucopurulent</td>
</tr>
<tr>
<td>Redness</td>
<td>Conjunctival</td>
<td>Conjunctival</td>
<td>Conjunctival et episcleral</td>
</tr>
<tr>
<td>Depth of ulcer</td>
<td>Superficial</td>
<td>Superficial</td>
<td>Crater</td>
</tr>
<tr>
<td>Corneal cellular infiltrates</td>
<td>None</td>
<td>None</td>
<td>Yes (grey border at ulcer’s edge)</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>Mild</td>
<td>Mild to severe</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Corneal blood vessels</td>
<td>None</td>
<td>Very little to several&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Very little to several&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anterior chamber cellular infiltrates</td>
<td>None</td>
<td>None</td>
<td>- Tyndall effect (aqueous flare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hypopyon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Keratite precipitates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Hyphema (especially with corneal rupture)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Miosis (can be severe)</td>
</tr>
<tr>
<td>Miosis (mild)</td>
<td>Miosis</td>
<td>Miosis</td>
<td>Miosis (can be severe)</td>
</tr>
</tbody>
</table>
a. Blepharospasm, epiphora, enophthalmos with prolapse of the third eyelid
b. Depending on chronicity

**DIAGNOSTIC TESTS**

**Schirmer Tear Test (STT)**
It is important to verify tear production, because it may be inadequate and could be the main reason for the fragility of the epithelial cells. A STT of 15 mm/min is not ‘normal’ in a case of corneal ulceration (especially if it is superficial, exposing nerve endings). Ocular pain causes excessive tearing, and patients with corneal ulcer should have a high STT. The exception to the rule of verifying tear production is in cases of complex ulcers, particularly a descemetocele. The application of the STT strip could create a corneal stress that would lead to the rupture of the cornea.

**Fluorescein Stain Uptake**
The retention of fluorescein on a cornea will be noted if there is bare corneal stroma exposed. The epithelium and Descemet’s membrane do not retain fluorescein. The exception to the rule of verifying retention of fluorescein is in cases of complex ulcers, particularly a descemetocele. Again, the handling required for the application of fluorescein could lead to rupture of the cornea. Furthermore, whether it is a descemetocele or a very deep ulcer, the therapy chosen will be the same.

**Corneal Debridement**
Following the application of topical anesthetic drops, corneal debridement of a simple ulcer will not dramatically enlarge its surface area (at most 1 mm). Corneal debridement of a recurring ulcer will remove a substantial amount of corneal epithelium, to such an extent that the diameter of the initial ulcer will be significantly expanded (2–5 times). Corneal debridement of complex ulcer is not recommended, because the depth of the ulcer may lead to rupture of the cornea due to the stress of debridement.

**Corneal Cytology**
To acquire a sample for corneal cytology, the “Microbrushes” are superior to any other instrument (scalpel blade, Kimura spatula, cotton swab). Following the application of 1–2 drops of topical anesthetic, the brush is lightly rubbed around the ulcer’s contour. The sample should not be spread from one side to the other of the microscope slide, but rather at the center of it. Diff-Quik staining or Gram staining can be used for the analysis of cells collected.

Corneal cytology is rarely used for simple and recurring ulcers, because the infection is not present. In an ideal world, all complex ulcers should be analyzed with corneal cytology, because the identification of the type of bacteria present (rods versus cocci; Gram-positive versus negative) can help in the choice of antibiotics. For example, identification of Gram-positive cocci suggests the administration of cefazolin (50 mg/ml), while the presence of Gram-negative rods suggests the use of an aminoglycoside or a fluoroquinolone. Only 4th-generation fluoroquinolones (moxifloxacin) are effective against Gram-positive bacteria.

**Corneal Culture**
Before taking the sample for an aerobic bacterial culture, the swab should be dipped in the transport medium in order to increase the chances of positive results. We also recommend that you take the sample prior to application of fluorescein, as it has antibacterial properties. The application of one drop of topical anesthetic should not influence the results. It is important to ensure that the selection of antibiotics analyzed is commercially available in solution or ointment. A call to the laboratory to select antibiotics will save time and frustration!

A bacterial culture is rarely done for simple and recurrent ulcers. However, in an ideal world, an aerobic culture sample should be collected for all complex ulcers. Anaerobic and fungal cultures are not
recommended routinely, because few cases are reported in dogs and cats. However, if the chosen therapy has disappointing results, a more advanced investigation including the submission of an anaerobic culture is reasonable.

**Polymerase Chain Reaction**
This test is especially reserved for viral infections. The detection of herpesvirus in the dog would be the primary indication for this test; we do not usually recommend this test in cats due to the high prevalence of herpes in cats.

**THERAPY FOR CORNEAL ULCERS**
There are several therapies for corneal ulcers. In some cases, beware of your initial analysis, as a simple ulcer may become a recurrent ulcer or complex in a short amount of time! Do not forget to correct (if possible) the underlying cause of the ulcer (entropion, ectopic cilia, KCS...).

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Simple ulcer</th>
<th>Recurrent ulcer</th>
<th>Complex ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical antibiotic</strong></td>
<td>Bacteriostatic&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of antibiotic administration</td>
<td>QID</td>
<td>QID</td>
<td>Minimum: q 6 hrs</td>
</tr>
<tr>
<td>Topical atropine 1% BID</td>
<td>If miosis</td>
<td>If miosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Artificial tears</td>
<td>If KCS</td>
<td>If KCS</td>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertonic saline (Muro-128)</td>
<td>No</td>
<td>On occasion</td>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum</td>
<td>No</td>
<td>?</td>
<td>Yes (with melting)</td>
</tr>
<tr>
<td>Corneal debridement</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Linear keratotomy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Contact lens</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Conjunctival or corneal graft</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic medications</td>
<td>No</td>
<td>NSAIDs&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Elizabethan collar</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- Examples: chloramphenicol, tetracycline, erythromycin
- Not recommended for cats (BNP: Hume-Smith et al., 2011); keratotomy may predispose to corneal sequestrum
- Examples: gentamicin, tobramycin, ciprofloxacin, ofloxacin, cefazolin
- Because several ophthalmic solutions will be put on the eye, the addition of artificial tears or Muro-128 brings little benefit and could dilute the drugs
- Carprofen (dog); meloxicam (dog/cat); Tolfedine (cat)
- Tramadol (dog); buprenorphine (cat)
- Only if risk of corneal rupture
**Viral Corneal Ulcers**

In cats, herpesvirus corneal ulcers are frequently diagnosed in private practice. The pathogenesis of the virus includes toxicity of conjunctival epithelial cells leading to conjunctivitis, toxicity of corneal epithelial cells leading to a superficial ulcer, and latent recurrence caused by the persistence of the virus in the trigeminal ganglion and the journey to and fro from the cornea through the CNV. Common clinical signs include conjunctivitis, punctate linear or geographical corneal ulcer, and symblepharon in affected kittens (from a severe infection).

In dogs, this virus has recently been investigated as a cause of conjunctivitis and corneal ulceration. Though the reactivation of the virus has not yet been demonstrated in scientific studies, a recurrence of clinical signs is possible, because this virus is known to take refuge in CNV in several species.

Diagnostic tests for cases of viral corneal ulcers are the same as those for bacterial corneal ulcers, because in the majority of cases a secondary bacterial infection is present. In cats, since herpes is common, PCR is rarely needed. In the dog, since the virus is diagnosed infrequently, PCR is recommended.

Antiviral drugs may be necessary therapy in viral corneal ulcers. The number of drugs needed to treat each case varies according to the severity of the symptoms.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Minor infection&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Moderate infection&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Severe infection&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical antibiotic&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Bacteriostatic QID</td>
<td>Bactericidal QID</td>
<td>Bactericidal q 2–4 hrs</td>
</tr>
<tr>
<td>Topical antiviral&lt;sup&gt;e&lt;/sup&gt;</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic antiviral</td>
<td>No</td>
<td>?</td>
<td>Hematology and liver enzyme follow-up</td>
</tr>
<tr>
<td>Famiciclovir (62.5–125 mg SID, BID)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>L-lysine&lt;sup&gt;f&lt;/sup&gt;</td>
<td>No</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Interferon 25–30 U PO 7 days on, 7 days off (2x) ? 25–50 U topical QID</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Artificial tears&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

- a. Conjunctivitis, linear superficial ulcer
- b. Moderate conjunctivitis, geographic superficial ulcer, secondary bacterial infection
- c. Severe conjunctivitis (with or without symblepharon), deep ulcer, secondary bacterial infection
- d. Chloramphenicol, tetracycline, erythromycin, BNP (dog only)
- e. Trifluridine (1 drop q 4 hrs for 4 days, then QID for 10 days); Ganciclovir (1 drop QID for 14 days); Cidofovir (1 drop BID for 14 days)
- f. To date, no study has been conducted on the effectiveness of lysine in dogs suffering from HCV
- g. Herpesvirus in cats is the main cause of KCS in this species

**REEVALUATIONS**

The frequency of cases of corneal ulcer reevaluations depends on the severity of each case. Simple ulcers should be reevaluated within 3–5 days from diagnosis to check the response to treatment; in this case, the retention of fluorescein should be almost zero! Recurrent ulcers may be reevaluated within 5–7 days; the retention of fluorescein should be 50% less than the diameter of the ulcer created by
debridement and linear keratotomy. Complicated ulcers should be reevaluated after 24 hours if the patient was not hospitalized. When you are sure that the infection is under control (ulcer not deepened or not widened and mucopurulent discharge flow is solved), a decrease in the frequency of topical drug delivery can have places, and reevaluations can be done 72 hours.

The decision to go to surgery depends on the depth of the ulcer (> 50% of the stroma). However, do not begin too quickly in surgery, because if the infection is not under control, stitches will be devoured by bacteria and collagenases! It is recommended to refer cases requiring a graft to a veterinary ophthalmologist. A third eyelid flap or a temporary tarsorrhaphy would be considered malpractice in the surgical management of complex ulcers. If financial concerns exist or poor owner/pet compliance is problematic, enucleation of a painful globe at risk of rupture should be recommended.

REFERENCES
Feline Ophthalmology
Chantale L. Pinard, DVM, MSc, DACVO
Although our feline friends have similar ocular pathologies as our canine friends, they also have a few distinct ocular conditions of their own. Cat eyes are not simply small dog eyes!

**EYELID DISEASES**

**Congenital**
**Eyelid coloboma** or eyelid aplasia is a partial absence of the palpebral margin, usually upper lateral eyelid. This eyelid condition can be bilateral and accompanied by corneal lesions (keratitis). This condition is often associated with concurrent intraocular abnormalities (optic nerve colobomas). The cause is genetic, a possible recessive gene, often seen in Persians. The diagnosis is by the examination of palpebral margins. Surgical correction is recommended. This can be done by reconstructing the upper eyelid margin (blepharoplasty) or by cryotherapy of skin edge (prevent regrowth of hair).

**Acquired**
**Blepharitis** is an inflammation of the eyelids. One common congenital presentation of blepharitis is ophthalmia neonatorum. This disease is a conjunctival infection prior to eyelid opening. An underlying infection of feline herpesvirus is suspected to be the cause in most cases. The diagnosis is by the clinical appearance of bulging of eyelids, +/- purulent discharge from a medial fistula. Culture of secretions is recommended for the best antimicrobial selection. Clavamox is usually the first-line systemic antibiotic chosen. If no opening is present at the medial canthus, then creation of such opening is recommended. Irrigation of the conjunctival fornix with diluted povidone-iodine 1:50 should be performed. Topical antibiotics such as chloramphenicol or tobramycin QID are also recommended. Lubrication of the cornea is also beneficial with artificial tears QID. Housing should be dim lit, as these young eyes are not ready for the light until 14 days of age.

Blepharitis can also be caused by parasites that result in focal areas of alopecia and crusting. The most common in cats is *Notoedres cati* (scabies). The diagnosis is by skin scrapings, and the treatment is ivermectin (off-label) (Ivomec). If one is brave, lime-sulfur dips (LymDyp) can also be done!

**CONJUNCTIVAL/CORNEAL DISEASES**

**Conjunctivitis**, a hyperaemia of the conjunctival blood vessels, can be a primary or secondary disease in cats (secondary to blepharitis, corneal ulceration, and uveitis). Conjunctivitis can be accompanied by a serous to mucopurulent discharge, chemosis, and keratoconjunctivitis sicca (KCS). The causes of primary conjunctivitis are feline herpesvirus-1 (FHV), *Chlamyphila*, *Mycoplasma*. Conjunctival cytology early in the infection can be diagnostic for all three pathogens; however, if confirmation is required, then polymerase chain reaction analysis is recommended for all three pathogens. Treatment for FHV is stated below (feline herpetic keratitis section). Treatment for *Chlamyphila* or *Mycoplasma* includes topical tetracycline, chloramphenicol, or erythromycin TID for 2–4 weeks or systemic tetracycline: 5 mg/kg BID 21 days (especially for *Chlamyphila*).

A **symblepharon** is one or several adhesion(s) between different locations of conjunctiva or conjunctiva to cornea. This ocular condition is a common sequela to severe FHV infections. Diagnosis is confirmed by the appearance of conjunctival adhesion(s), especially involving the third eyelid. Treatment is aimed at FHV and the second bacterial infection present (see feline herpetic keratitis section). Surgical correction can be difficult and may not be rewarding, as a recurrence of FHV may occur due to the stress of anesthesia and hospitalisation.

**Feline herpetic keratitis** has been described as causing dendritic corneal ulcers; however, superficial geographical ulcers are the norm with an accompanying conjunctivitis and KCS. Following primary infection, FHV-1 which resided in trigeminal ganglia and travels up CNS following reactivation of
latent virus triggered by stress. The diagnosis can be confirmed by cytology (predominantly PMN, intranuclear bodies at initial infection). Indirect fluorescent antibody (IFA) - remember to not stain beforehand (false positive) - and PCR can also be done to confirm diagnosis.

Treatment options are the following:

<table>
<thead>
<tr>
<th>Topical antibiotics</th>
<th>Mild infection(^a)</th>
<th>Moderate infection(^b)</th>
<th>Severe infection(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes QID</td>
<td>Yes QID</td>
<td>Yes q 4–6 h QID</td>
<td></td>
</tr>
<tr>
<td>Topical antivirals(^g)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic antivirals(^f)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic l-lysine(^e)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic NSAIDs(^h)</td>
<td>No</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Topical artificial tears</td>
<td>Yes QID</td>
<td>Yes QID</td>
<td>?</td>
</tr>
</tbody>
</table>

a. Mild infection: conjunctivitis, serous to mucoid to mucopurulent ocular discharge, no corneal ulceration  
b. Moderate infection: conjunctivitis, mucopurulent discharge, corneal ulcer, miosis  
c. Severe infection: conjunctivitis, chemosis, mucopurulent discharge, corneal ulcer (superficial or deep), corneal oedema and neovascularisation, miosis  
d. Topical antibiotics: chloramphenicol for mild infection and Tobramycin for moderate to severe infection; avoid BNP due to potential for anaphylaxis  
e. Topical antivirals: Viroptic q 4 h for 4 days, then QID for 10 days or ganciclovir QID 14 days or Cidofovir BID 14 days  
f. Systemic antivirals: famciclovir 62.5–125 mg/cat SID–BID for 14–21 days  
g. Systemic l-lysine: 500 mg BID during active infection  
h. Systemic NSAIDs: meloxicam one injection, Tolfedine 4 mg/kg SID 4 days, Deramaxx 4 mg/kg SID 5 days

**Feline stromal keratitis** is part of the syndrome of FHV; however, the virus is embedded into the stroma, and the clinical signs are more severe. Corneal scarring is more severe following remission. Diagnosis and treatment are similar to those for severe infection with feline herpetic keratitis.

**A corneal sequestrum** is a black, brown or rust-coloured lesion composed of necrotic stroma usually seen in Persians and Himalayans. This condition has also been linked to FHV, especially in domestic cats. A genetic cause is suspected in Persians and Himalayans. Diagnostic tests include STT, fluorescein stain uptake (+ at edges), and PCR FHV (especially in domestic cats). The recommended treatment is a keratectomy +/- conjunctival or graft. Medical therapy (topical antibiotics) until the sequestrum sloughs off can also be done in cases unable to be referred.

**Eosinophilic keratitis** is a progressive vascular and eosinophilic infiltration into the corneal stroma resulting in pink to white corneal plaques. The cause has been linked to FHV, but the condition is not related to eosinophilic syndrome in cats. The diagnosis is by corneal cytology (eosinophil, mast cell, and lymphocyte). Treatment varies depending on fluorescein stain uptake: if fluorescein positive or unknown FHV status, then topical chloramphenicol and trifluridine 2-week treatment; if fluorescein and herpes negative, then topical: 0.1% dexamethasone BID–TID. Subconjunctival steroids (betamethasone, triamcinolone) q 4 weeks can also be done in uncooperative cats. Treatment is life-long; however, some cases can go into remission for several months.

**Bullous keratopathy** is a severe corneal oedema resulting in keratoconus. This condition can be unilateral or bilateral. Although the exact cause is unknown, the condition is similar to the Manx’s
stonal dystrophy. Fluorescein stain uptake should be done to ascertain the integrity of the cornea. Treatment includes Muro-128 q 4 hours and topical antibiotic. Some reports suggest a third eyelid flap or conjunctival graft to help with the corneal oedema.

**Uveal Diseases**

Although anterior and/or posterior uveitis is seen in dogs, cats have their own particular causes. As with dogs, trauma (corneal ulcer, blunt or penetrating) is the leading cause of uveitis. Idiopathic causes make up for several cases. Infectious causes include: FIP, FIV, toxoplasmosis, and Cryptococcus. Melanoma, adenoma/carcinoma, and lymphoma (FeLV) are the main neoplastic causes. Cataracts are the main immune-mediated cause of uveitis in cats.

The clinical signs are various and may include: aqueous flare, keratic precipitates fibrin, hypopyon, iritis, iridal nodules, iridal hyperaemia, vitreitis, and retinal detachments/haemorrhage/infiltrates. Ocular pain (prolapse of third eyelid/squinting/tearing) is seen in several cases; the severity of the clinical signs depends on the severity of the uveitis.

The classic diagnosis of uveitis is the finding of low intraocular pressures (< 10 mm Hg); however, intraocular pressures can rise into the range of glaucoma if the uveitis is severe. Depending on the underlying cause suspected, different diagnostic tests may be required.

Standard treatment for uveitis is the inclusion of corticosteroids (topical, subconjunctival, or systemic). Topical 1% prednisone acetate or 0.1% dexamethasone can be given BID in mild cases to q 2 hours in severe cases. Atropine 1% should be given BID until pupillary dilatation, then as needed.

The author recommends consulting review articles on feline uveitis for in-depth specifics on diagnostic tests and treatment options (see References section).

**Glaucoma**

There are 2 types of glaucoma: primary (congenital and genetic: uncommon) and secondary (uveitis, aqueous misdirection, neoplasia: common). Congenital glaucoma can be seen in kittens less than 6 months of age. Uveitis, independent of its underlying cause, is the leading cause of glaucoma in cats. Aqueous misdirection is a phenomenon seen in older cats where the aqueous humour does not filter through the pupil toward the iridocorneal angle but is directed caudally to the vitreous; this misdirection causes an increase in volume in the vitreal chamber and a rostral displacement of the iris-lens diaphragm.

Cats do not show the same degree of pain with glaucoma than most dogs, and pupillary dilatation may not be as prominent in this species. Buphthalmia only occurs with congenital glaucoma (due to young elastic sclera) or due to chronic glaucoma. The diagnosis is confirmed with tonometry (> 30 mm Hg).

Therapeutic options are limited in cats, as uveitis is the main cause of glaucoma. Mannitol (1 g/kg IV) over 20–30 minutes and water withheld for 2–3 hours is a temporary solution. Available anti-glaucoma drugs are the following: topical carbonic anhydrase (Trusopt or Azopt TID–QID) or beta blockers (timolol BID). The use of topical beta blockers is problematic for asthmatic cats! The use of topical corticosteroids QID will also help diminish IOP due to the underlying uveitis. Enucleation should be recommended if the eye is not responsive and painful.

**Retinal Diseases**

**Nutritional retinal degeneration** entails the deficiency of taurine, an essential amino acid for photoreceptors. This is a disease of the past, since commercial diets are well supplemented; however, still it may occur with stray cats or cats fed homemade diets not well balanced. It is reported that retinal degeneration can occur after 23 weeks of deficiency.
The diagnosis is first suspected with a granular appearance of area centralis. If the deficiency is not addressed, an ellipsoidal hyperreflective lesion and a large band-shaped hyperreflective area will appear with attenuation/loss of retinal blood vessels.

Treatment consists of supplementation with 500–750 ppm SID of taurine. Supplementation may reverse ERG findings but not fundic lesions and will not reverse blindness if present.

**Rod-cone dysplasia/degeneration** is a rare condition in cats, except in the Abyssinian. Dysplasia is inherited as autosomal dominant where kittens (4 wks) progress to blindness by 1 year of age. Degeneration is inherited as autosomal recessive where adult cats (2 years of age) progress to blindness over 2–4 years.

Diagnosis is suspected in cats that have tapetal hyperreflectivity, loss of pigmentation in non-tapetum, and attenuation of retinal blood vessels.

Unfortunately, there are no effective treatments, and the recommendation is to avoid breeding affected cats.

**Retinal toxicity secondary to Baytril** presents as an acute blindness due to retinal degeneration following high levels of enrofloxacin administration (> 5 mg/kg/day). Blindness can occur at any time following administration of Baytril. It is thought that high plasma level of enrofloxacin in susceptible cats leads to apoptosis of retinal cells.

Diagnosis is suspected with a history of Baytril administration associated with the appearance of tapetal hyperreflectivity and blood vessel attenuation on fundic exam. To arrive at a conclusive diagnosis, one must eliminate all other causes of retinal atrophy (i.e., secondary to retinal detachment, retinal hemorrhages...). An ERG will confirm low to absent retinal function in these cases.

Treatment consists of stopping the administration of the antibiotic. Vision may return in some cases, but blindness may also be permanent.

**Neoplasia**

**Squamous cell carcinoma** of the eyelids is the most common ocular tumours in cats. The lesions are usually erosive but may also be nodular in appearance. It is thought that actinic radiation on poorly pigmented eyelids leads to the development of this tumour.

The diagnosis is confirmed by skin biopsy.

Therapeutic options usually consist of surgical excision with margins + cryotherapy, radiation, or CO₂ laser ablation of the margins. Unfortunately, there are high levels of recurrence if margins are not clean.

The **diffuse melanoma of the iris** is the most common intraocular tumour in cats. This tumour has a potential of becoming malignant. The brown hyperpigmentation spots on the iris appear as freckles but can start to coalesce and multiply in numbers with time. At this time, there are no known underlying causes or factors that promote the development of this tumour.

The diagnosis can be confirmed by fine-needle aspirate (or vacuuming) of the iris (can be unrewarding) or iris biopsy (invasive procedure).

The classic therapy is to watch and wait or enucleation. The risks of metastasis should be explained to the owner; however, this tumour can be slow to metastasize, and the patient may die of other causes prior to this tumour causing serious metastatic disease. In young cats, diode laser photocoagulation of hyperpigmented spots is controversial and yet unproven; however, for some owners, this treatment option (that has shown positive results in dogs) can be promising in keeping a visual eye pain-free for longer periods of time. Enucleation is necessary if glaucoma is present or if the tumour is noted in the iridocorneal angle.

**Traumatic intraocular sarcoma** is a feline phenomenon that can occur years after the initial traumatic event (proptosis, blunt or perforating trauma). This malignant tumour, once detected, has a grave prognosis, as the survival rate drops to weeks–months. It is theorized that intraocular trauma in
the past with possible lens capsule rupture and lens epithelial migration lead to the development of this tumour.

The diagnosis is suspected with an intraocular mass with hyphema and/or glaucoma. The definitive diagnosis is achieved with histopathology.

To palliate that ocular pain, enucleation is recommended.

REFERENCES

Emergency Ophthalmology: Dos and Don’ts!
Chantale L. Pinard, DVM, MSc, DACVO

Ocular emergencies can be very stressful and challenging for the veterinarian due to the possibility of impending vision loss. A good initial examination is mandatory in order to gather as much information as possible to adequately assess the ocular condition. It is needless to say that an ocular exam sheet is a must and that drawings may give more information than the written word! Before starting the ocular exam, common sense dictates certain rules to live by....

**Rules To Live By**
- Acute presentation of ocular disease may quickly lead to vision loss
- Minimize manipulation of ocular tissues as much as possible, because they are very reactive
- The affected eye may be quite painful...muzzle if needed, sedation if needed
- Minimize further potential ocular trauma with an Elizabethan collar
- Third eyelid flap does not prevent corneal perforation
- Complete ocular exam (as much as possible) is a must!
- **Do not forget to examine the “good” eye!**
  - Diagnostic tests:
    - Pupillary light reflexes (direct and consensual) are a must!
    - Schirmer Tear Test if risk of perforation is absent
    - Fluorescein stain if risk of perforation is absent
    - Intraocular pressures if risk of perforation is absent
    - Corneal cytology, aerobic culture and sensitivity if infection is suspected
- Postoperative care:
  - Better to reevaluate sooner than later
  - Almost all patients should leave with an E. collar!

I) Trauma

A) Proptosis

A proptosis is an acute forward displacement of the globe beyond the bony orbit and eyelid margins with rolled inward eyelids preventing return of the globe to a normal position. The extraocular muscles may be damaged, leading to a deviation of the globe.

The clinical signs may include exophthalmos, conjunctival hyperemia, conjunctival/subconjunctival hemorrhage, chemosis, corneal desiccation/ulceration, intraocular hemorrhage, uveitis, blindness.

The diagnostic tests that should be performed at minimum are pupillary light responses and fluorescein stain uptake. A miotic pupil has best prognosis; a midsize has guarded prognosis; and dilated pupils have grave prognosis.

Treatment can only be started once the patient is stabilized. This may mean chest radiographs for patients hit by car. During stabilisation, keep the cornea lubricated (sterile K-Y Jelly, Teargel, Optixcare). Patients with a ruptured globe or optic nerve severed or three extraocular muscles severed should have their eye enucleated. If a blood clot is in the anterior chamber, consider referral to a veterinary ophthalmologist for an injection of tissue plasminogen activator into the anterior chamber to dissolve the clot.

For eyes that have been deemed salvageable, a temporary tarsorrhaphy should be done. This entails the following: general anesthesia, lateral canthotomy, gentle manipulation of eyelids to unroll and cover the globe, and placement of 2–3 horizontal mattress sutures (4-0 silk or Prolene) through stents and use meibomian gland openings as landmarks. A **3rd eyelid flap is not strong enough to keep the globe in position**. If strabismus is noted due to an avulsed extraocular muscle, attempting to
resuture muscle and replace globe in normal position can be very frustrating (medial rectus is usually the first to rupture, but may be difficult to find muscle remnants). Leave a small opening by medial canthus for medication. Topical triple antibiotic solution QID to q 4 hrs, topical atropine BID (avoid using topical steroids or NSAIDs, as a corneal ulcer may develop later due to corneal desiccation). Systemic antinflammatory drugs (carprofen 2 mg/kg BID 5–7 days; meloxicam for small dogs; Tolfedine or Deramaxx for cats) should be prescribed unless patient is already being treated with systemic steroids. Systemic antibiotics include Clavamox for 10–14 days. Recommend a recheck in 2 days since eyelid inflammation may subside and sutures may subsequently rub on cornea. Leave the tarsorrhaphy for 14–21 days and place E. collar to prevent further trauma. Remove sutures earlier if persistent pain, copious mucopurulent discharge, fever. Sequelae include blindness, strabismus, phthisis bulbi (may take weeks to occur due to ongoing uveitis), glaucoma....Never promise vision since prognosis at best is guarded!

Consider referral if unable to deal with patient in the following hours, poor comfort level of surgeon with enucleation surgery, and considering suturing of avulsed or partially ripped extraocular muscles.

B) Lid Injuries
Eyelid lacerations and bite wounds should be examined and repaired as soon as possible (within 6 hrs), as inflammation and oedema will distort tissues and make the repair more challenging.

The clinical signs include eyelid swelling +/- hemorrhage, loss of tissue from eyelids.
A fluorescein stain should be performed to verify the integrity of the cornea.

Treatment includes carefully clipping the eyelids, clean with Betadine scrubs and follow up with sterile saline and 0.5% Betadine solution (be careful not to put Betadine scrub on cornea). Minimal wound debridement (avoid additional loss of tissue) is required, as eyelids are well vascularised. Suture conjunctiva with 5-0, 6-0 Vicryl simple-continuous pattern; invert sutures in order to protect cornea and if conjunctiva too traumatized, just suture skin. Start to suture at eyelid margin and place simple-interrupted sutures 3 mm apart with 4-0 or 5-0 Prolene; excellent apposition of palpebral margins is a must! Prescribe topical antibiotics without steroids if a corneal ulcer is present (or with steroids if intact cornea) TID–QID until recheck. Systemic antibiotics should be given (Clavamox, cephalixin) (7–10 days). Systemic antinflammatory drugs (carprofen) (3–5 days) will help with pain and inflammation of the eyelids. Recommend recheck 3 days later, as swelling may have subsided and sutures may be loose and need readjustments. Remove skin sutures in 14 days.

Consider referral if unable to deal with patient in a timely manner, if the eyelids are severely damaged, or either canthi needs to be reconstructed.

C) Corneal Injuries
Corneal injuries vary from superficial abrasions to full-thickness lacerations. They can also include foreign body impalement. The patient is usually very painful, and application of topical anaesthesia +/- sedation may be required. Penetrating and perforating injuries should be surgically addressed ASAP by a veterinary ophthalmologist (preferably within 6 hours of the accident). While awaiting therapy, the patient should be wearing an E. collar.

The clinical signs include ocular discharge (clear, hemorrhagic, mucopurulent), corneal oedema, +/- iris protrusion and hyphema.

The diagnostic tests are the following: pupillary light reflexes (check for indirect/consensual response - very important!); aerobic culture; corneal cytology (Gram stain if possible); fluorescein stain if the risk of rupture is low; and ocular ultrasound - if suspect possible lens injury with corneal perforation (should be done very delicately!).

The treatment varies with the extent of the trauma. Prepping of the cornea should be done with dilute Betadine solution 1:50 and sterile saline. For corneal laceration or corneal perforation, enucleation should be done if intraocular contents are protruding through large corneal defect (4–5
mm), globe is severely deformed, indirect PLR not present, financial restrictions. Offer referral if the PLR present and owner wishes to “do everything.” Do not attempt to remove fibrin plug until surgery. If lens is damaged, refer to a veterinary ophthalmologist for therapy. The corneal defect may require conjunctival graft. Topical bactericidal antibiotic q 2 hrs until sensitivity results should be started. Topical atropine BiD should be given if miosis is present. An E. collar should be placed on the patient. Systemic NSAIDs such as carprofen/meloxicam PO BiD should be started.

If a corneal foreign body is present, topical anesthesia and sedation +/- general anaesthesia may be required. Cut over the length of the FB in order to remove it. Do not pull on it, as it may break! Topical antibiotics to consider are gentamicin, tobramycin or ciprofloxacin qID. Atropine BiD should be given as the removal of the foreign body will be painful and create a reflex uveitis. If plant material is left in the cornea, it may lead to fungal keratitis. Again, an E. collar is a must.

Superficial ulcers can be treated with topical triple antibiotic qID, atropine BiD and recheck in 3–5 days with E. collar.

Deep ulcers should have a culture and sensitivity submitted prior to therapy. Topical antibiotic selection entails the following: if Gram-negative: gentamicin 1 drop q 2–4 hrs, if Gram-positive: ciprofloxacin or cefazolin (50 mg/ml) 1 drop q 2–4 hrs. Again, topical atropine BiD, carprofen/meloxicam PO, and E. collar should be prescribed. Rechecks are recommended every 4 hrs, but if a descemetocele is diagnosed, then every 24 hrs.

Melting ulcers should have the same therapy as above for deep ulcers, with the addition of autogenous serum (0.2 ml) q 2 hrs. Pull blood, let stand for 30 min, centrifuge, collect serum in red top tube, refrigerate between applications, replenish in 48 hrs (or sooner if contaminated). We recommend keeping the patient in hospital until globe appears stable and then recheck in 1 week.

Chemical keratitis should be treated as a corneal ulcer. Alkaline substances cause more damage than acids. Advise owner to flush eye with large amounts of 0.9% saline ASAP - not to wait until in your clinic. If alkaline substance involved, you can try a boric acid wash to neutralize reaction. If melting of the cornea is present, autogenous serum (see above) should be given. Topical triple antibiotics q 2–4 hrs, topical atropine BiD, systemic NSAIDs, and E. collar should be prescribed. We recommend a recheck in 24 hrs.

Consider referral if 24-hr care is not possible for deep ulcers or descemetoceles and/or corneal laceration or perforations. Cytology and culture can be done prior to referral and information transferred once received by the laboratory. If referral is delayed, aggressive medical therapy can be started in private practice.

II) INTRAOCULAR DISEASE

A) Glaucoma

The true ocular emergency since it is ultimately a blinding disease in almost all cases! Intraocular pressures (IOP) > 30 mm Hg (normal IOP 15–25 mm Hg) should be considered pathological and require immediate investigation since glaucoma is one of the leading causes of blindness in dogs and causes severe ocular pain.

Types of Glaucoma

It is important to recognize the type of glaucoma each patient may present with since it will impact the treatment regimen. Glaucomas can be categorized based on their inciting causes such as congenital, primary and secondary.

Congenital glaucoma can be a very early form of primary glaucoma or just an error that Mother Nature performed on a specific iridocorneal angle! This type of glaucoma can arise in any breed of young age and lead to a rapid onset of buphthalmia since the sclera is still in its growing phase and very elastic. Unfortunately, the prognosis for this type of glaucoma is almost always grave and requires enucleation.
**Primary glaucoma** is usually breed-specific and considered an inherited trait in several breeds such as the Cocker spaniels, Basset, Poodles, Chows, Shar Pei.... A useful tip is to have a list of the “hot breeds” handy in your treatment room or even framed in your reception area! Elevations of the intraocular pressures for 24–72 hrs can result in permanent blindness in the affected eye. Remember, in almost all cases of primary glaucoma, it is only a matter of time before the second eye becomes affected!

**Secondary glaucoma** is due to an anterior lens luxation, neoplasia, or severe uveitis. Terriers are genetically predisposed to lens luxation, and therefore all cases of glaucoma in terriers are generally suspected as secondary to lens displacement. Another tip is if a purebred dog - not one on the “hot list for glaucoma”- presents with high intraocular pressures, uveitis should be high on the list of causes. This is not to say that if the patient is not on the list, primary glaucoma is impossible.

Acute clinical signs of glaucoma include the following: “red” eye (episcleral injection +/- conjunctivitis); diffuse corneal oedema (mild, moderate or severe); fixed dilated pupil; +/- optic disc cupping; vision loss (especially if the first eye has lost the glaucoma battle); and ocular pain (blepharospasm, lacrimation, protrusion of third eyelid, change in personality or normal behaviour).

Chronic clinical signs include the following: buphthalmia (enlarged globe); keratitis from exposure; corneal striae (breaks in the Descemet’s membrane); diffuse corneal oedema moderate to severe); fixed dilated pupil; lens luxation may be present; retinal atrophy and optic disc cupping; and vision loss.

The diagnostic tests include a neuro-ophthalmic exam, tonometry (normal range: 15–25 mm Hg).

**An important factor to consider when commencing treatment is the type of glaucoma present in the patient in front of you. The first step is to reduce the intraocular pressures ASAP!**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Primary glaucoma</th>
<th>Possible lens subluxation</th>
<th>Uveitis</th>
<th>Feline glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>2nd line</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prostaglandin analogue</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

a. Primary glaucoma: no uveitis and/or lens luxation or subluxation

In rare cases, the intraocular pressures can be decreased with a paracentesis of aqueous humour. This is a very controversial method of reducing intraocular pressures and should only be considered as a salvage procedure. Improper technique can lead to disastrous situations.

Aqueocentesis: 30 g ½-inch needle placed at lateral limbus and letting 1–3 drops of fluid drip out of the hub.

**Reperfusion Injury**

Reperfusion injury is thought to occur after rapid decompression of the globe; our present treatments can reduce the pressure in the globe in less than 1 hour and therefore predispose the globe to this type of injury. Unfortunately, there are no canine studies to date that have identified efficacious neuroprotectors. However, there are anecdotal reports of using systemic calcium channel blockers (i.e., amlodipine for one week) and/or corticosteroids (0.5 mg/kg PO prednisone or 0.25 mg/kg IV dexamethasone) to reduce oxidative stress from the release of radicals after decompression.
Maintenance Therapy (Until Referral)
The intraocular pressures should be measured every hour until 25 mm Hg is reached for at least 2 consecutive hours. Topical carbonic anhydrase inhibitors can be used every 6–8 hrs, topical beta blockers every 12 hrs, and prostaglandin analogues every 12–24 hrs. Once the IOP is within normal range, recheck IOP at 4–6 hr interval initially and determine cause for glaucoma (i.e., primary versus secondary). If IOP is stable for 24 hrs, refer to a veterinary ophthalmologist if possible. Regular monitoring depends on cause of glaucoma and response to treatment. Recommend educating your clients on the signs of glaucoma and have them verify pupillary light reflexes (flashlight test).

Not all drugs mentioned are indicated for your patient if...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>Diabetes, renal failure, cardiomyopathy, dehydration</td>
</tr>
<tr>
<td>Travatan, Xalatan</td>
<td>Uveitis, lens luxation</td>
</tr>
<tr>
<td>Timolol</td>
<td>Cardiomyopathy, asthma</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>Renal failure, cardiomyopathy, dehydration</td>
</tr>
</tbody>
</table>

Surgical Treatment of Glaucoma
Unfortunately, medical therapy may only control the IOP for a certain time period, and most cases of glaucoma eventually become nonresponsive to medical therapy. Prompt referral to a veterinary ophthalmologist should be recommended to all owners in order for them to have as many options as possible to choose from for their pet. Surgical options will depend on the status of the eye in question. Painful blind eyes that are refractory to medical therapy should be enucleated, eviscerated with implantation of a silicone prosthesis, or have an intravitreal injection of gentamicin (25 mg) and dexamethasone (2 mg). All of the aforementioned techniques have their risks and benefits.

With primary glaucoma where the eye is still visual, other surgical procedures, such as ciliary body photocoagulation or anterior chamber shunt placement, can be done to prolong vision. These surgical procedures should be done by a veterinary ophthalmologist since the risks and complication rate can sometimes be very challenging to manage. Unfortunately, even with surgical therapies, vision loss is a question of time. Studies have shown that in primary glaucoma, medical therapy of the still non-affected “good” eye is warranted and may delay the onset of glaucoma in this eye. There are several therapies recommended, but the one suggested by this author is dorzolamide or brinzolamide twice daily with regular IOP rechecks (once monthly). Again, this therapy will only delay the onset of glaucoma, but hopefully the owner as well as the family veterinarian will be on the lookout for early signs of ocular hypertension (conjunctival hyperaemia, sluggish PLR, change in behaviour...).

With secondary glaucoma, the ultimate therapy is to find the primary cause. If uveitis is suspected, blood tests such as CBC, serum biochemistry profile, heartworm test, tick titres..., chest radiographs and abdominal ultrasound may be necessary to detect the underlying systemic disease. Aggressive topical (prednisone acetate 1% q 4–6 hrs) and systemic corticosteroids (1–2 mg/kg/day PO) may be warranted especially if posterior uveitis with retinal detachment is seen. If intraocular neoplasia is suspected, enucleation is the only recommended therapy; this also entails sending the globe for histopathology.

Feline Glaucoma
Most if not all feline cases of glaucoma are secondary to uveitis. Uveitis, especially chronic cases, damages the iridocorneal angle and leads to increased intraocular pressures. Cats appear to be more pain tolerant than their canine counterparts, and the clinical signs sometimes are not as apparent. It is amazing at times that they can retain a PLR with high pressures! A diagnostic workup including toxoplasmosis titres, FIV/FeLV titres, and complete blood work should be done. Unfortunately, many cases are idiopathic, and antiinflammatory therapy is recommended. If medical therapy fails to control the intraocular pressures, enucleation is usually recommended as surgical treatment; evisceration with
intraocular prosthesis is an alternative treatment. Unfortunately, only in few selected cases would the gentamicin injection be suggested; a risk of traumatic sarcomas could arise with this therapy.

**B) Uveitis**
A “red eye” can be due to various diseases that are unrelated to each other. The “redness” must be appropriately identified and localised to the conjunctiva, sclera, cornea, anterior chamber, and/or iris.

Emergency cases of hyphema or intraocular hemorrhage can be dramatic in appearance. Hyphema can have several causes, such as uveitis, systemic hypertension, coagulopathy, trauma, and neoplasia. Hyphema can quickly resolve in 24 hrs, especially if bleeding has stopped and is due to a coagulopathy. Hyphema can quickly lead to glaucoma if trauma is the cause, as fibrin will also have leaked into the anterior chamber and the ensuing blood clot may lead to a pupillary block.

**Dos and Don’ts**

<table>
<thead>
<tr>
<th>Do</th>
<th>Don’t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete ocular exam: neuro-ophthalmic exam, STT, fluorescein stain uptake, intraocular pressures</td>
<td>Start topical corticosteroids until fluorescein stain uptake is known</td>
</tr>
<tr>
<td>Diagnostic workup: Doppler measurement of blood pressure, CBC, ACT, physical examination, and ocular ultrasound</td>
<td>Start topical atropine until intraocular pressures are known</td>
</tr>
</tbody>
</table>

Consider referral to a veterinary ophthalmologist if access to an ocular ultrasound is limited. If aggressive medical therapy is warranted due to the severity of the uveitis, 24-hr care may be required and therefore referral to an ER clinic is warranted.

**C) Anterior Lens Luxation**
Primary lens luxation can cause secondary glaucoma due to pupillary block and/or obstruction of iridocorneal angle. Canine breeds at risk include terriers. In cats, chronic uveitis is usually the cause of zonular degeneration leading to luxation. Chronic glaucoma with associated buphthalmia can also lead to secondary luxation. A more favorable outcome is seen with these cases if IOP is within normal range and short duration of symptoms.

The clinical signs include scleral and conjunctival hyperemia, corneal edema (focal or diffuse), lens in anterior chamber, and/or deep ant. chamber if posterior luxation.

The main diagnostic tests include a neuro-ophthalmic exam and tonometry.

Initial treatment includes treating glaucoma if present (see above) and timely referral for intracapsular lens extraction.

**III) ACUTE BLINDNESS**
The main rule-outs for acute blindness are: glaucoma, retinal detachment, sudden acquired retinal degeneration, immune-mediated retinitis, optic neuritis, and cortical blindness. As loss of vision is devastating to an owner, prompt referral to a veterinary ophthalmologist is recommended.

**A) Retinal Detachment**
Bilateral retinal detachment leads to acute vision loss. The main causes for this syndrome are: systemic hypertension (first differential), uveitis (systemic inflammatory/infectious diseases), coagulopathies, severe trauma, and breed disposition: Shih Tzu, Bichon, German Shepherd.... Prognosis for vision is guarded since it will depend on degree of retinal detachment (partial vs. complete), duration, and cause. With Shih Tzus, one eye may detach first, and the dog continues to function normally in the household; it is when the second retina detaches that a vision problem is noted by owners.

The clinical signs include: abnormal PLR (may be present but sluggish or incomplete), dilated pupils, retinal vasculature seen through pupil, and gray veil seen on fundic exam if complete detachment.
The main ocular diagnostic tests include neuro-ophthalmic exam and tonometry. Other diagnostic tests include systemic blood pressure (especially cats), CBC, serum biochemistry profile, and thorough physical exam.

The underlying cause should be addressed. For example, cases of uveitis should have systemic steroids (prednisone 1 mg/kg BID until reattachment, then wean off) and amlodipine for systemic hypertension. Cases where a retinal tear has led to the retinal detachment will require retinal reattachment surgery; prompt referral to a qualified veterinary ophthalmologist is recommended as soon as possible. However, if the retinal detachment is bullous, then diode laser barrier retinopexy can be done by most veterinary ophthalmologists to prevent progression of the detachment.

B) Sudden Acquired Retinal Degeneration
Acute vision loss (within 1 day to 1 week) is the usual presentation of this syndrome in dogs only. It is seen most likely in overweight, middle-aged, female dogs according to the literature; it is also questionably associated with Cushing’s and/or hypothyroidism.

The clinical signs include absent to slow/weak PLR, absent menace response and dilated pupils in normal light.

As the fundic exam is normal, the recommended diagnostic test is an electoretinogram.

Unfortunately, there are no reliable treatments at this time, and vitamin supplements can be suggested (Ocu-GLO: www.ocuglo.com).

C) Immune-Mediated Retinitis
Immune-mediated retinitis cannot be distinguished from SARDs on ocular examination (see clinical signs above). The electoretinogram will show poor, but present, function in one or both eyes. The good news is that return of vision can occur in some cases with treatment of oral prednisone 1 mg/kg/day and doxycycline 5 mg/kg/day. If vision is to return, it usually does within 5–7 days from start of therapy. Oral prednisone can be exchanged with oral cyclosporine or azathioprine. As with all immune-mediated diseases, weaning of medication cannot be done quickly, as relapses of blindness can occur. With each relapse of blindness, the prognosis for return of vision diminishes.

D) Optic Neuritis
Optic neuritis can present solely as a loss of vision. In most cases, an infectious or neoplastic cause is found in the patient. The main cause listed in the literature is granulomatous meningoencephalitis (GME). Unfortunately, the prognosis for return of vision is guarded at best and is usually poor.

Consultation with a neurologist may be helpful to determine other concurrent CNS disease.

The clinical signs include hemorrhagic or oedematous optic nerve head, +/- retinal detachment (focal to optic nerve head), and +/- retinal haemorrhage (surrounding optic nerve head).

The main diagnostic test recommended is a thorough fundic exam following pupillary dilation with tropicamide. Advanced imaging with an MRI is also recommended in consultation with a veterinary neurologist.

Treatment consists of systemic corticosteroids (prednisone 1 mg/kg/day 5–7 days, then taper dose accordingly).

E) Cortical Blindness
Blindness has been documented in cases of patients experiencing status epilepticus. Return of vision is unknown for the first 10 days - if blindness is still present after 10 days from the seizure, then prognosis for return of vision is grave. Consultation with a veterinary neurologist is highly recommended.

REFERENCES
Ocular Manifestation of Systemic Diseases
Chantale L. Pinard, DVM, MSc, DACVO

When faced with a patient affected by a systemic disease, the inclusion of a complete ocular exam can reveal valuable data, as there is no other body system where vasculature and extracellular space can be evaluated directly and noninvasively. For example, through a clear cornea, anterior chamber and lens, the central nervous system and peripheral vasculature can be assessed.

Certain infectious agents, immune-mediated syndromes, and metastatic tumours can be diagnosed or confirmed via examination of ocular tissues and/or sampling of ocular media. Certain systemic diseases may also affect specific ocular parameters, such as tear production and quality, which can then lead to ocular conditions requiring therapy.

The main message of this lecture is the following: if you diagnose any of the systemic diseases listed below, have a look at the eyes! Keep in mind that ocular clinical signs may be the first symptom of a systemic disease!

INFECTIOUS
There are several infectious agents that may inflict damage to ocular tissues. Revelation of the specific agent can be achieved by sampling ocular tissues followed by polymerase chain reaction, cytology or histopathology analysis, or by sampling ocular media followed by cytology or culture. Therapy is aimed at the infectious agent at cause, but in most cases, ocular inflammation will also need treatment, as it is mostly the inflammation - not the agent - that destroys ocular tissues (see last table).

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>Ocular clinical signs</th>
<th>Ocular diagnostic test(s)</th>
<th>Ocular therapy</th>
<th>Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canine distemper</td>
<td>- Mucopurulent discharge&lt;br&gt;- Conjunctivitis&lt;br&gt;- Optic neuritis (blindness)</td>
<td>- STT&lt;br&gt;- Fluorescein stain&lt;br&gt;- IFA on conjunctiva</td>
<td>- Optimmune BID&lt;br&gt;- Topical antibiotic QID&lt;br&gt;- Systemic NSAIDs&lt;br&gt;- Artificial tears QID</td>
<td>Permanent KCS</td>
</tr>
<tr>
<td>Canine herpesvirus</td>
<td>- Conjunctivitis&lt;br&gt;- Ulcerative keratitis</td>
<td>- STT&lt;br&gt;- Fluorescein stain&lt;br&gt;- Conjunctival PCR, IFA</td>
<td>- Topical antibiotic QID&lt;br&gt;- Artificial tears QID&lt;br&gt;- Topical antiviral&lt;br&gt;- Systemic NSAIDs&lt;br&gt;- Oral L-lysine?</td>
<td>Recurrent infections</td>
</tr>
<tr>
<td>Infectious canine hepatitis</td>
<td>- Corneal oedema&lt;br&gt;- Uveitis</td>
<td>- STT&lt;br&gt;- Fluorescein stain&lt;br&gt;- Tonometry (IOP)</td>
<td>- Topical Muro-128 QID&lt;br&gt;- Topical corticosteroids if no ulcers&lt;br&gt;- Topical antibiotics if ulcers QID&lt;br&gt;- Topical atropine</td>
<td>Permanent corneal oedema&lt;br&gt;- Chronic corneal ulcerations</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td><strong>Ehrlichiosis (E. canis)</strong></td>
<td>- Uveitis</td>
<td>- Fluorescein stain</td>
<td>- Topical corticosteroid</td>
</tr>
<tr>
<td>- Hyphema</td>
<td>- Retinal hemorrhages</td>
<td>- Tonometry (IOP)</td>
<td>- Topical atropine</td>
<td>- Systemic corticosteroid</td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td>- Uveitis</td>
<td>- Fluorescein stain</td>
<td>- Topical corticosteroids</td>
<td>- Glaucoma</td>
</tr>
<tr>
<td>- Hyphema</td>
<td>- Retinal hemorrhages</td>
<td>- Tonometry (IOP)</td>
<td>- Topical atropine</td>
<td>- Systemic corticosteroids</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Uveitis</td>
<td>- Fluorescein stain</td>
<td>- Topical corticosteroids</td>
<td>- Glaucoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tonometry (IOP)</td>
<td>- Topical atropine</td>
<td>- Blindness</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Uveitis</td>
<td>- Fluorescein stain</td>
<td>- Topical corticosteroids</td>
<td>- Glaucoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tonometry (IOP)</td>
<td>- Topical atropine</td>
<td>- Blindness</td>
</tr>
</tbody>
</table>

| **Fungal** | - Blastomycosis | - Uveitis | - Fluorescein stain | - Topical corticosteroids | - Cataracts |
| - Histoplasmosis | - Retinal granulomas | - Optic neuritis | - Topical atropine | - Glaucoma |
| - Coccidiomycosis | - Subretinal cytology | - Intravitreal voriconazole injection | - Systemic corticosteroids | - Retinal detachment |

| **Algae** | Protothecosis | - Uveitis | - Fluorescein stain | - Topical corticosteroids | Death |
| | - Retinal granulomas | - Tonometry (IOP) | - Systemic corticosteroids | |
| | - Subretinal cytology | |

<p>| <strong>Protozoa</strong> | Toxoplasmosis | - Uveitis | - Fluorescein stain | - Topical corticosteroids | - Cataracts |
| | - Optic neuritis | - Tonometry (IOP) | - Topical atropine | - Glaucoma |
| | - Clindamycin | - Blindness |
| Leishmaniasis | - Blepharitis | - Fluorescein | - Topical | - Recurrent |</p>
<table>
<thead>
<tr>
<th>Parasite</th>
<th>Diseases</th>
<th>Signs</th>
<th>Diagnostic Tests</th>
<th>Therapy</th>
<th>Sequelea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dirofilariasis</td>
<td>Conjunctivitis</td>
<td>- Flourescein stain</td>
<td>- Tonometry (IOP)</td>
<td>- Topical corticosteroids</td>
<td>Recurrent infections</td>
</tr>
<tr>
<td>(heartworm)</td>
<td>Ulcerative keratitis</td>
<td></td>
<td></td>
<td>- Topical atropine</td>
<td>Cataracts</td>
</tr>
<tr>
<td></td>
<td>Stromal keratitis</td>
<td></td>
<td></td>
<td>- Systemic corticosteroids</td>
<td>Glaucoma</td>
</tr>
<tr>
<td></td>
<td>Worm in anterior chamber</td>
<td></td>
<td></td>
<td>- Systemic NSAIDs</td>
<td>Phthisis bulbi</td>
</tr>
</tbody>
</table>

**STT, Schirmer Tear Test; IFA, indirect fluorescein antibody; KCS, keratoconjunctivitis sicca; IOP, intraocular pressure; PCR, polymerase chain reaction; NSAIDs, nonsteroidal antiinflammatory drugs**

**Cats**

**Infectious disease**

**Viral**

**Feline herpesvirus**

- Conjunctivitis
- Ulcerative keratitis
- Stromal keratitis
- STT
- Fluorescein stain
- Conjunctival PCR
- Conjunctival IFA
- Topical atropine QID
- Artificial tears QID
- Systemic corticosteroids
- Cataracts
- Glaucoma
- Phthisis bulbi
- Blindness

**Feline immunodeficiency virus**

- Uveitis
- Retinal detachment
- Fluorescein stain
- Systemic corticosteroids
- Cataracts
- Glaucoma
- Phthisis bulbi
- Blindness

**Feline leukemia virus**

- Uveitis
- Retinal detachment
- Fluorescein stain
- Systemic corticosteroids
- Cataracts
- Glaucoma
- Phthisis bulbi
- Blindness

**Feline infectious peritonitis**

- Uveitis
- Retinal granulomas
- Fluorescein stain
- Systemic corticosteroids
- Cataracts
- Glaucoma
- Phthisis bulbi
- Blindness

**Bacterial**

- Chlamydiosis
- Mycoplasmosis
- Conjunctivitis
- STT
- Fluorescein
- Topical chloramphenicol,
- KCS
- Symblepharon
stain
- Conjunctival cytology
- Conjunctival PCR
erthyromycin
- Artificial tears
- Systemic doxycycline

**Fungal**
- Cryptococcosis
  - Uveitis
- Blastomycosis
  - Retinal granulomas
- Histoplasmosis
  - Optic neuritis
- Coccidiomycosis
  - Fluorescein stain
  - Topical corticosteroids
  - Cataracts
- Topical corticosteroids
- Systemic corticosteroids
- Glaucoma
- Retinal detachment
- Blindness
- Tonometry (IOP)
- Intravitreal voriconazole injection
- Blindness

**Protozoa**
- Toxoplasmosis
  - Uveitis
  - Optic neuritis
  - Fluorescein stain
  - Clindamycin
  - Cataracts
  - Glaucoma
  - Blindness
- Topical corticosteroids
- Systemic corticosteroids
- Glaucoma
- Blindness
- Tonometry (IOP)
- Recurrent infections
- Glaucoma
- Phthisis bulbi
- Blindness

**Leishmaniasis**
- Blepharitis
  - Conjunctivitis
- Keratitis
- Uveitis
- Retinal detachment
- Fluorescein stain
- Topical corticosteroids
- Systemic corticosteroids
- Recurrent infections
- Glaucoma
- Phthisis bulbi
- Blindness
- Tonometry (IOP)

**IMMUNE-MEDIATED**
Immune-mediated diseases that are commonly seen with ocular conditions involve either the eyelids or the uveal tract. Dogs are more prone than cats to immune-mediated diseases leading to ocular diseases. As seen with several infectious systemic diseases, the uveal inflammation resulting from immune-mediated diseases needs to be addressed promptly. The severity of the ocular clinical signs, as well as the systemic signs will dictate the frequency and dosing of antiinflammatory and immunomodulating medications.

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>Ocular clinical signs</th>
<th>Ocular diagnostic test(s)</th>
<th>Ocular therapy</th>
<th>Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pemphigus foliaceus</td>
<td>- Blepharitis</td>
<td>- STT</td>
<td>Systemic corticosteroids</td>
<td>- Facial dermatitis</td>
</tr>
<tr>
<td>- Lupus discoid</td>
<td>- Conjunctivitis</td>
<td>- Fluorescein stain</td>
<td>- Artificial tears</td>
<td>- Tear film instability</td>
</tr>
<tr>
<td>- Allergies</td>
<td>- Blepharitis</td>
<td>- STT</td>
<td>- Topical NSAIDs</td>
<td>- Recurrences</td>
</tr>
<tr>
<td>- Atopy</td>
<td>- Conjunctivitis</td>
<td>- Fluorescein stain</td>
<td>- Topical corticosteroids</td>
<td>- Facial dermatitis</td>
</tr>
<tr>
<td></td>
<td>- Follicular conjunctivitis 3rd eyelid</td>
<td></td>
<td></td>
<td>- Chronic blepharitis</td>
</tr>
</tbody>
</table>
Uveodermatological syndrome (VKH) - Depigmentation of eyelids - Depigmentation of uvea - Uveitis - Fluorescein stain - Tonometry (IOP) - Topical corticosteroids - Topical atropine - Systemic corticosteroids - Systemic azathioprine - Systemic cyclosporine - Chronic epiphora - Glaucoma - Retinal detachment - Blindness

- Immune-mediated anemia - Uveitis - Fluorescein stain - Tonometry (IOP) - Ocular ultrasound - Topical corticosteroids - Topical atropine - Systemic corticosteroids - Systemic azathioprine - Systemic cyclosporine - Glaucoma - Retinal detachment - Retinal atrophy - Blindness

- Immune-mediated thrombocytopenia - Uveitis - Hyphema - Artificial tears TID - Systemic corticosteroids - Enophthalmia - Visual deficits

Myositis - Acute exophthalmos - Chronic enophthalmos - Fluorescein stain - Topical corticosteroids - Artificial tears TID - Systemic NSAIDs if ulceration - Systemic corticosteroids - Chronic epiphora - KCS - Cataract - Retinal detachment

METABOLIC
There are several metabolic diseases that can manifest in ocular diseases. Diabetes mellitus, Cushing’s disease, and hypothyroidism in the dog will affect the quantity and quality of tears, leading to poor corneal health and a predisposition to corneal ulcers. The aforementioned diseases as well as hyperlipidemia may also lead to corneal lipid deposition. These corneal deposits are white in colour, and their presence may weaken the cornea and predispose it to ulceration. Taurine deficiency of more than 23 weeks can lead to visual deficits.

<table>
<thead>
<tr>
<th>Metabolic disease</th>
<th>Ocular clinical signs</th>
<th>Ocular diagnostic test(s)</th>
<th>Ocular therapy</th>
<th>Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (dog)</td>
<td>- KCS - Corneal ulcers - Cataract - Lens-induced uveitis - Blindness</td>
<td>- STT - Fluorescein stain - Tonometry (IOP)</td>
<td>- Optimmune - Artificial tears if ulcer - Topical NSAIDs if uveitis - Systemic NSAIDs if ulceration</td>
<td>- Chronic ulcers - KCS - Cataract - Lens rupture - Glaucoma - Retinal detachment</td>
</tr>
<tr>
<td>Condition</td>
<td>Signs and Symptoms</td>
<td>Treatments</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Cushing's disease (dog)</td>
<td>- Corneal ulcers</td>
<td>- STT</td>
<td>Chronic ulcers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Corneal lipid deposits</td>
<td>- Fluorescein stain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Lipemia retinalis</td>
<td>- Optimmune</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Retinal detachment if systemic hypertension</td>
<td>- Artificial tears</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism (dog)</td>
<td>- Corneal ulcers (indolent)</td>
<td>- STT</td>
<td>Chronic ulcers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Corneal lipid deposits</td>
<td>- Fluorescein stain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia (dog)</td>
<td>Corneal lipid deposits (white)</td>
<td>- STT</td>
<td>Chronic ulcers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fluorescein stain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Optimmune</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia (dog and cat)</td>
<td>Cataracts</td>
<td>- Fluorescein stain</td>
<td>Cataracts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Topical steroids if uveitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension (dog and cat)</td>
<td>- Mydriasis</td>
<td>Tonometry (IOP)</td>
<td>Permanent blindness or visual deficits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hyphema</td>
<td>- Amlodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Blood clot in anterior chamber</td>
<td>- Consult internal medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Slow to absent PLR</td>
<td>- Blood clot in anterior chamber</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Retinal detachment</td>
<td>- Slow to absent PLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Retinal hemorrhages</td>
<td>- Retinal detachment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taurine deficiency (cat)</td>
<td>- Mydriasis in severe cases</td>
<td>Tonometry (IOP)</td>
<td>Blindness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hyperreflective focus in retina</td>
<td>- Supplementation of taurine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Visual deficits</td>
<td>- Supplementation of taurine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Blindness</td>
<td>- Blindness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Neoplasia**

Secondary or metastatic neoplasia to the eye can be seen in both dogs and cats. The most common metastatic neoplasm is **lymphoma** in both pet populations. Hemangiosarcoma, transmissible venereal tumour, adenocarcinoma, sarcoma, chondrosarcoma, carcinoma, and osteosarcoma have been reported in the literature as metastatic ocular tumours. As the eye has a high flow rate, it is not without reason that tumour cells would be presented to the uveal tract and infiltrate the eye. Most intraocular tumours will present with a uveitis, which can entail a mass effect within the eye, hyphema, aqueous flare, and/or retinal detachment and/or hemorrhage.

As stated above, a complete ocular exam is warranted, as uveitis could trigger a secondary glaucoma. Ocular ultrasound is a valuable tool to investigate the uveal tract and search for tumours. Consultation with a veterinary oncologist is paramount prior to starting any therapy. Topical
corticosteroids could impact the diagnosis of systemic lymphoma. Once a diagnosis is established, topical corticosteroids should be started to control the secondary uveitis. Painful ocular globes due to metastatic disease cannot be adequately controlled with oral opioids, steroids or NSAIDs. If the globe is indeed painful and the animal is stable for general anesthesia, discussion with the owner regarding enucleation should take place, especially if the patient has several weeks or months to live.

Although granulomatous meningoencephalitis (GME) is not considered by some to be neoplastic but inflammatory in nature, GME is an important systemic disease that likely possesses an ocular component. This disease is the leading cause of visual deficits or blindness in dogs with retinal granulomas or optic neuritis. Consultation with a veterinary neurologist is paramount in these cases, and advanced imaging will help distinguish the extent of the disease. Systemic corticosteroids will help with the posterior uveitis and optic neuritis; however, other treatment modalities will be suggested by a veterinary neurologist. Unfortunately, if the patient presents with blindness due to an optic neuritis, the prognosis of return of vision is grave.

**Nonspecific Therapy for Uveitis Secondary to a Systemic Disease**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids</td>
<td></td>
<td>Do not use on corneal ulcers</td>
</tr>
<tr>
<td>Prednisone acetate 1%</td>
<td>BID–QID</td>
<td>Can be given q 1 hour if needed</td>
</tr>
<tr>
<td>Dexamethasone 0.1%</td>
<td>BID–QID</td>
<td>Not as powerful as prednisolone acetate?</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.5–1 mg/kg/day</td>
<td>May need higher dose if immune-mediated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lowest dose is 0.25 mg/kg/day</td>
</tr>
<tr>
<td>Topical NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>BID–TID</td>
<td>Do not use on corneal ulcers</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>BID–TID</td>
<td>Not as powerful as diclofenac</td>
</tr>
<tr>
<td>Systemic NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carprofen</td>
<td>&lt; 2 mg/kg BID</td>
<td>More economical in large dogs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not labelled for cats</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>&lt; 0.1 mg/kg/day</td>
<td>Easier dosing for small dogs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be used once in cats</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>&lt; 4 mg/kg/day</td>
<td>Labelled for 7 days in medium to large dogs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New formulation available for cats for 6 days</td>
</tr>
<tr>
<td>Tolfenamic acid</td>
<td>&lt; 4 mg/kg/day</td>
<td>Labelled for 5 days in dogs and cats</td>
</tr>
<tr>
<td>Topical mydriatics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine 1%</td>
<td>BID–PRN</td>
<td>Once pupil is dilated, then on an “as-needed” basis, as iris sphincter muscle is now paralyzed</td>
</tr>
<tr>
<td>Tropicamide 1%</td>
<td>BID–QID</td>
<td>Not as powerful as atropine</td>
</tr>
</tbody>
</table>
REFERENCES

Ocular Pharmacology: When to Use What?
Chantale L. Pinard, DVM, MSc, DACVO
The general principles of ocular pharmacology will be explored during this lecture. Only the most commonly prescribed medications in practice will be presented and discussed.

Routes of Application of Ocular Medication

Topical Solutions
As the majority of common ocular diseases occur in the anterior segment of the eye, the most common formulation of ophthalmic drugs is drops applied topically to the eye. When applied, topical solutions mix with the tear film and a portion is absorbed by the conjunctiva and cornea while another portion (80%) is carried away into the nasolacrimal system. Systemic absorption of topical solutions can be clinically significant, as seen in cases of systemic hypertension following instillation of 10% phenylephrine in small/toy patients, corticosteroid in diabetic patients, beta blockers in cardiac patients. Although contact time may be as short as 30 seconds, it is estimated that topical ophthalmic drops are absorbed within 5 minutes of administration. Therapeutic levels of ophthalmic drops can be detected in the anterior chamber and as far posterior as the ciliary body; however, adequate drug concentrations may not reach the posterior segment tissues.

The general rule of thumb for application is that one drop is sufficient per treatment since the conjunctival fornix can only accommodate an additional 10–25 µl of additional fluid in the tear film. As the maximum volume of the conjunctival fornix is 30 µl after drop instillation, the dosing of one drop (50 µl) far exceeds what amount can be contained. Waiting 5–10 minutes between drops is recommended for optimal absorption (no dilution effect from other topical medications). Of important note, aqueous suspensions require repeated shaking of the bottle (40 times) for maximal deliverable effects. For ease of identification, caps and bottles of topical ophthalmic solutions are colour-coated: mydriatics and cycloplegics are red, miotics are green, carbonic anhydrase inhibitors are orange, beta-adrenergic blockers are yellow or blue, antimicrobials are tan or brown, nonsteroidal antiinflammatory drugs (NSAIDs) are grey, and glucocorticoids are pink.

Topical Ointments
Topical ophthalmic ointment counterparts exist for several topical ophthalmic solutions. Ointments have several advantages over solutions, which include longer contact time of drug to surface tissues (therefore potentially fewer treatments per day), lack of dilution by tears, smaller amount of drug entering the nasolacrimal system (therefore potentially less systemic effects), and lubrication and protection of the cornea due to its petroleum vehicle. Blinking boosts the release of drug from ointments. Only a small amount of ointment (0.5- to 1-cm strip) is needed per treatment, and waiting 20–30 minutes between applications is recommended to avoid dilution effect from other topical medications. However, ointments are not without their disadvantages, which include a higher incidence of contact dermatitis, higher toxicity to the corneal endothelium if corneal perforation is present, increased amount of ocular discharge, higher incidence of tube contamination, limited choice of medications, and challenging application for some owners. Furthermore, although longer contact time is cited as an advantage, drug release from the vehicle (i.e., its availability) can be unpredictable for certain medications.

Subconjunctival Injections
A subconjunctival injection of soluble medication can be carried out in cooperative small animal patients following topical anesthesia; a 25-g needle is recommended, and a total volume of 0.1–0.5 ml can be easily injected. The medication is injected beneath the bulbar conjunctiva and rests upon the sclera where a portion of drug is absorbed. This transscleral absorption bypasses dilution of tears and corneal
barriers; it allows medication to enter the anterior chamber and penetrate the anterior uvea. Leakage of the drug through the injection hole also occurs, and a portion of the drug is absorbed by the conjunctiva and cornea. Subconjunctival injections are usually seen as a supplemental therapy to increase drug concentrations at the level of the anterior segment. Common medications administered by this route include mydriatics, antibiotics, and corticosteroids. Care must be taken to choose the appropriate formulation in order to avoid ocular irritation (i.e., preservative-free solutions). Subconjunctival injections are not without risk, and these include accidental perforation of the globe, local irritation, increased systemic absorption with associated potential side effects, and inability to stop absorption of repositol products once injected.

Systemic Medications
Systemic medications such as tablets, capsules, oral liquid suspensions, and intravenous solutions are used to effectively treat ocular diseases that occur in orbital tissues, eyelids, sclera, conjunctiva, uvea, retina, and optic nerve. As with most other tissues in the body, vascularised ocular tissues attain therapeutic drug levels if drug absorption and bioavailability are optimal for the patient. Common examples include systemic antibiotics for eyelid infection, corticosteroids or NSAIDs for uveitis, and mannitol for glaucoma.

ANTIMICROBIAL DRUGS

Antibacterial Drugs
Topical antibiotics are commonly used to treat conjunctival and corneal infectious diseases. Topical antibiotics should be instilled a minimum of 4 times daily and may require administration every 4 hours in severe infections. Broad-spectrum antibiotics such as triple-antibiotic preparations should be used as first line if the infection is mild to moderate and the infectious agent is unknown. Topical triple-antibiotic formulations can be found in ointment preparations. The ointment preparations contain neomycin and polymyxin-B, the latter effective against *Pseudomonas* spp. Aminoglycosides are bactericidal antibiotics that are commonly used in cases with infected corneal ulcers. Resistance of certain organisms such as *Pseudomonas* spp., *S. aureus*, *Aerobacter*, *Klebsiella* spp. and *Proteus* spp. to gentamicin has occurred over the years due to its popular use. Resistance to tobramycin is not as common, and tobramycin is less epitheliotoxic than other bactericidal antibiotics. Topical fluoroquinolones have gained popularity in practice due to their effectiveness. However, fluoroquinolones have been shown to lack effectiveness against streptococci, and resistance can occur to other bacteria. Only fourth-generation fluoroquinolones (moxifloxacin) have efficacy against some Gram-positive bacteria. Careful monitoring should be done when using fluoroquinolones, as it has been reported that they inhibit keratocyte proliferation and produce cytotoxicity in culture preparations. This, in turn, can potentially cause a deep corneal ulcer to progress to a descemetocoele. Topical antibiotics should be continued until fluorescein stain uptake is negative.

Systemic antibiotics are indicated for posterior segment infections. Amoxicillin-clavulanic acid combination antibiotics are the first-line choice for bacterial blepharitis and orbital abscess/cellulitis. Aminoglycosides are rarely used systemically due to their nephrotoxicity and ototoxicity. Systemic fluoroquinolones are usually reserved for when antibiotic sensitivity results are known. Enrofloxacin, a systemic fluoroquinolone, has been linked with acute blindness in cats.

<table>
<thead>
<tr>
<th>Topical drugs</th>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td>Bactericidal</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1 drop q 4–6 hours</td>
<td>Can be epitheliotoxic</td>
</tr>
<tr>
<td>Neomycin</td>
<td>1 drop q 4–6 hours</td>
<td>Component of triple antibiotic</td>
</tr>
</tbody>
</table>
Tobramycin 1 drop q 4–6 hours Less epitheliotoxic

**Fluoroquinolones**

Ciprofloxacin 1 drop q 4–6 hours Available as ointment, 2nd generation
Moxifloxacin 1 drop q 4–6 hours Newest on the market, 4th generation
Ofloxacin 1 drop q 4–6 hours Penetrates cornea well, 2nd generation

**Miscellaneous**

Chloramphenicol 1 drop or ½-cm strip QID Bacteriostatic Effective against *Chlamydia* and *Mycoplasma*
Bacitracin ½-cm QID Bactericidal Component of triple antibiotic
Gramicidin 1 drop QID Component of triple antibiotic
Polymyxin-B 1 drop or ½-cm strip QID Bactericidal Component of triple antibiotic
Tetracycline ½-cm strip QID Bacteriostatic Effective against *Chlamydia* and *Mycoplasma* Can be irritating

**Antiviral Drugs**

Topical antiviral drugs are typically first-line drugs prescribed in cases of feline herpesvirus infection. They are reserved for cases that have corneal ulcerations, severe chemosis, conjunctivitis, and/or symblepharon development.

Systemic antiviral drugs are available for feline herpesvirus infections. Acyclovir is no longer prescribed, as it has questionable benefits and serious toxicity in cats. Famciclovir has gained popularity in treating severe, chronic or stromal feline herpesvirus keratitis. However, it is recommended to monitor blood counts and liver enzymes throughout the therapy.

L-lysine, in an oral supplement formulation, has been used extensively in the adjunct therapy of feline herpesvirus infections. Although not proven effective as a dietary supplement in Humane Society settings, it has been shown to decrease the severity of clinical signs in primary infections and reduce viral shedding in latent infections.

<table>
<thead>
<tr>
<th>Topical drugs</th>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine arabinoside 3%</td>
<td>½-cm strip q 4 hours</td>
<td>Moderately effective Not irritating</td>
</tr>
<tr>
<td>Cidofovir 0.5%</td>
<td>1 drop q 12 hours</td>
<td>Moderately effective Can be epitheliotoxic</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>1 drop QID</td>
<td>Modestly effective</td>
</tr>
<tr>
<td>Trifluridine 1%</td>
<td>1 drop q 4 hours, then q 6 hours for 10 days</td>
<td>Very effective Less toxic Can be irritating Expensive</td>
</tr>
</tbody>
</table>

**Systemic drugs**

<table>
<thead>
<tr>
<th></th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
**Topical Antiseptics: Povidone-Iodine**

Diluted povidone-iodine solution (1:25, 1:50) is the preferred germicide for prepping of ophthalmic surgical patients. This solution is bactericidal, viricidal and fungicidal. Although well tolerated by most patients, allergic reactions such as chemosis and conjunctivitis have been noted in a very small number of patients. For this reason, the 1:50 dilution is recommended for flushing of the conjunctival fornix. This solution can also be used in the therapy of infected tissues such as corneal ulcers. Following sampling and prior to instillation of topical antibiotics, topical diluted povidone-iodine can be used to “clean or flush” away microbial agents from the infected tissues.

**Topical Antiinflammatory Drugs**

**Corticosteroids**

Topical corticosteroids are mainly prescribed for chronic superficial keratitis, atopic conjunctivitis, and idiopathic or immune-mediated uveitis. Topical and systemic corticosteroids are contraindicated with diabetic patients and corneal ulcerations. Topical corticosteroids can promote corneal deposition of calcium and lipid with chronic use. Topical corticosteroids can also induce iatrogenic Cushing’s syndrome and adrenal gland suppression.

Subconjunctival injections of corticosteroids are usually performed with suspensions that leave a deposit under the conjunctiva. Absorption from these suspensions can be slow and maintain therapeutic drug levels for several weeks. The main advantage of these injections is the reduction of topical administration of steroids in difficult patients; however, the main disadvantage occurs if this patient develops a corneal ulcer and healing is negatively impacted.

Systemic administration of corticosteroids is primarily carried out to treat inflammatory conditions of the orbit, sclera, uvea, retina and optic nerve. Systemic corticosteroids are commonly prescribed for retinal detachment due to immune-mediated causes. Although they can be prescribed to treat infectious causes of retinal detachment, risks and benefits must be weighed for every case and the lowest dose used (i.e., prednisone 0.25–0.5 mg/kg/day). Due to their clinical side effects (polydipsia/polyuria, panting, lethargy, gastrointestinal disturbances) and systemic side effects (increase in liver enzymes, adrenal gland suppression), the lowest effective dose is recommended.

<table>
<thead>
<tr>
<th>Topical drugs</th>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone alcohol 0.1%</td>
<td>1 drop q 1–24 hours</td>
<td>2nd-best antiinflammatory effect</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>NA</td>
<td>Lowest potency (ineffective)</td>
</tr>
<tr>
<td>Prednisone phosphate 0.1%</td>
<td>1 drop q 1–24 hours</td>
<td>3rd-best antiinflammatory effect</td>
</tr>
<tr>
<td>Prednisolone acetate 1%</td>
<td>1 drop q 1–24 hours</td>
<td>Best antiinflammatory effect; vigorous shaking required</td>
</tr>
<tr>
<td><strong>Subconjunctival drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone sodium</td>
<td>Injection every 1–2 weeks</td>
<td>Extremely potent</td>
</tr>
<tr>
<td>Dexamethasone phosphate</td>
<td>Injection every 1–2 weeks</td>
<td>Extremely potent</td>
</tr>
<tr>
<td>Methylprednisolone acetate</td>
<td>Injection every 2–4 weeks</td>
<td>Moderately potent</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Injection every 1–4 weeks</td>
<td>Moderately potent</td>
</tr>
<tr>
<td><strong>Systemic drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.05–0.25 mg/kg/day</td>
<td>Side effects still possible with lower doses</td>
</tr>
</tbody>
</table>
Prednisone 0.25–1.0 mg/kg/day Side effects still possible with lower doses

**Nonsteroidal Antiinflammatory Drugs**
Topical NSAIDs are used preoperatively in cataract surgery, in patients with nonulcerative keratitis (pigmentary or vascular), and in patients with uveitis. Topical NSAIDs are **contraindicated** in cases of corneal ulceration, glaucoma, and coagulopathies. Systemic NSAIDs are mostly prescribed for inflammatory conditions that include eyelids and orbital tissues including eyelids, and postoperative adnexal surgeries. They are also commonly used in diabetic patients.

<table>
<thead>
<tr>
<th><strong>Topical drugs</strong></th>
<th><strong>Systemic drugs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac 1 drop q 6–24 hours</td>
<td>Carprofen Dog: 2.2 mg/kg per os BID Hepatotoxicity</td>
</tr>
<tr>
<td>Ketorolac 1 drop q 6–24 hours</td>
<td></td>
</tr>
<tr>
<td>Nevanac 1 drop q 8–24 hours</td>
<td>Flunixin Dog: 0.25–1.0 mg/kg/day IV, SC, IM for 1–3 Off-label use</td>
</tr>
<tr>
<td>Suprofen 1 drop q 6–24 hours</td>
<td>meglumine treatments GI ulceration</td>
</tr>
<tr>
<td></td>
<td>Cat: 0.25 mg/kg SC once Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen 0.5–1 mg/kg BID per os GI ulceration</td>
</tr>
<tr>
<td></td>
<td>Meloxicam Dog: 0.2 mg/kg (induction dose) GI ulceration</td>
</tr>
<tr>
<td></td>
<td>0.1 mg/kg q 24 hours (maintenance)</td>
</tr>
<tr>
<td></td>
<td>Cat: 0.1 mg/kg single dose</td>
</tr>
<tr>
<td></td>
<td>Tolfenamic acid 4 mg/kg/day SQ or IM (once) followed by Not available in USA</td>
</tr>
<tr>
<td></td>
<td>4 mg/kg/day for 2–4 days</td>
</tr>
</tbody>
</table>

**TOPICAL ANTI-GLAUCOMA MEDICATION**
The lowering of IOP is mainly done by manipulating the outflow or production of aqueous humour and/or by reducing the intraocular fluid volume with osmotic diuretics. Topical medications carry fewer side effects than systemic drugs and therefore are preferred for most cases.

**Prostaglandin Analogues**
Prostaglandin analogues are effective topical anti-glaucoma drugs due to their ability to decrease IOP by increasing the uveal-scleral outflow in dogs; this class of anti-glaucoma medications is not effective in cats. Drugs in this class are best reserved for canine primary glaucoma. The effect of this medication can be seen within 30–60 minutes. Conjunctival hyperemia is usually apparent following administration. An important side effect of this class of medications is a severe miosis lasting 12–18 hours. Another side effect to consider prior to prescription is that they cause a breakdown of the blood-aqueous barrier; canine patients with glaucoma secondary to uveitis or lens luxation should not be prescribed these medications.

<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Frequency of administration</strong></th>
<th><strong>Comments</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bimatoprost 0.003%</td>
<td>1 drop q 12–24 hours</td>
<td></td>
</tr>
<tr>
<td>*Latanoprost 0.005%</td>
<td>1 drop q 12–24 hours</td>
<td>Requires refrigeration</td>
</tr>
<tr>
<td>*Travoprost 0.004%</td>
<td>1 drop q 12–24 hours</td>
<td></td>
</tr>
<tr>
<td>Unoprostone 0.15%</td>
<td>1 drop q 12–24 hours</td>
<td></td>
</tr>
</tbody>
</table>
*Latanoprost and travoprost are commonly prescribed for our canine patients, and they are typically at a frequency of every 24 hours.

**Carbonic Anhydrase Inhibitors**
Carbonic anhydrase inhibitors decrease IOP by lowering the production of aqueous humour within the eye. Although the effect of this drug class is not as rapid as prostaglandin analogues or osmotic diuretics (~1–2 hours), this class of drugs remains an important adjunct therapy for primary and secondary glaucoma in both dogs and cats. Topical formulations moderately decrease IOP. No effects on pupil size or blood-aqueous barrier are seen with this class of medication. The main advantage of topical formulations is the far fewer side effects compared to systemic counterparts.

<table>
<thead>
<tr>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical drug</strong></td>
<td></td>
</tr>
<tr>
<td>Brinzolamide 1%</td>
<td>1 drop q 6–8 hours</td>
</tr>
<tr>
<td>Dorzolamide 2%</td>
<td>1 drop q 6–8 hours</td>
</tr>
<tr>
<td>Methazolamide 2%</td>
<td>1 drop q 6–8 hours</td>
</tr>
</tbody>
</table>

**Systemic drug**

<table>
<thead>
<tr>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide 10–20 mg/kg q 8–12 hours</td>
<td>Many side effects</td>
</tr>
<tr>
<td>Methazolamide 2–5 mg/kg q 8–12 hours</td>
<td></td>
</tr>
</tbody>
</table>

**Beta-Adrenergic Drugs**
Beta-adrenergic blockers, or beta blockers, decrease IOP by lowering the production of aqueous humour. A very modest decrease in IOP has been reported in both dogs and cats with topical beta blockers. A positive additive effect is seen with combinations of beta blockers and carbonic anhydrase inhibitors. Mild miosis can occur with these medications in both species. An important side effect with these medications is bradycardia; this author has had cardiac patients on topical beta blockers experience worsening of their cardiac disease.

<table>
<thead>
<tr>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td></td>
</tr>
<tr>
<td>Betaxolol 0.5%</td>
<td>1 drop q 12 hours</td>
</tr>
<tr>
<td>Carteolol 2%</td>
<td>1 drop q 12 hours</td>
</tr>
<tr>
<td>Levobetaxolol 0.5%</td>
<td>1 drop q 12 hours</td>
</tr>
<tr>
<td>Levobunolol 0.5%</td>
<td>1 drop q 12 hours</td>
</tr>
<tr>
<td>Metipranolol 0.3%</td>
<td>1 drop q 12 hours</td>
</tr>
<tr>
<td>*Timolol 0.5%</td>
<td>1 drop q 12 hours</td>
</tr>
</tbody>
</table>

**Combination products**

<table>
<thead>
<tr>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosopt</td>
<td>1 drop BID–TID</td>
</tr>
<tr>
<td>DuoTrav</td>
<td>1 drop SID–BID</td>
</tr>
</tbody>
</table>

*Timolol 0.5% is commonly prescribed for our patients.

**Diuretics**
Osmotic diuretics can be effective at lowering IOP by reducing the aqueous and vitreous volumes within the eye. The effect of diuretics can be seen as early as 10 minutes but is usually detectable within 20–30 minutes and can last 5–12 hours. These medications are contraindicated in patients with congestive heart failure, systemic hypertension, renal insufficiency, and diabetes mellitus.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>1–2 g/kg IV over 20–30 minutes</td>
<td>Restrict water consumption for 2–3 hours; keep in fluid warmer to prevent crystallization of the solution</td>
</tr>
<tr>
<td>Glycerin</td>
<td>1–2 g/kg per os</td>
<td>Vomiting occurs if solution is not diluted</td>
</tr>
</tbody>
</table>
**MYDRIATIC AND CYCLOPLEGIC DRUGS**

Drugs that dilate the pupil are termed mydriatics, and drugs that paralyze the pupillary sphincter and ciliary muscle are termed cycloplegics. A sympathomimetic drug causes the iris dilator muscle to contract and results in mydriasis. Parasympatholytic drugs paralyze the pupillary sphincter muscle, causing mydriasis. With very young animals, drug-induced pupillary dilation with parasympatholytics is not as maximal or as long-lasting as compared to adults; for maximal pupillary dilation, use of sympathomimetics may be needed.

**Phenylephrine**

Phenylephrine is a direct-acting alpha-agonist sympathomimetic. Its main use is to help lesion localization in Horner’s syndrome. In dogs, 10% phenylephrine will dilate a pupil in a patient with a postganglionic lesion within 10–20 minutes. In cats, 1% phenylephrine will dilate a pupil in a patient with a postganglionic lesion, whereas preganglionic, central and normal eyes will not dilate. This topical drug will also aid in pupillary dilation in the normal dog but remains ineffective in the normal cat. Care must be taken when selecting the drug concentration, as 10% topical phenylephrine will increase systolic blood pressures in small/toy dogs and cats.

**Atropine**

Atropine is a parasympatholytic drug with both mydriatic and cycloplegic properties. On average, atropine’s onset of action is 1 hour, but duration of action can last 4–5 days. Atropine is commonly used in patients with uveitis (primary or secondary to corneal ulcers). Side effects of topical atropine include a transient decrease in tear production, hypersalivation if drainage through the nasolacrimal system enters the mouth, tachycardia, decreased gastrointestinal motility and photophobia due to prolonged dilatation. Hypersalivation is a common finding immediately following topical application of ophthalmic solution in cats. Long-term topical administration of atropine in young cats can result in smaller resting pupils following cessation of therapy. If severe uveitis with intense miosis is present, atropine may need to be frequently administered (q 6–12 hours) in order for the pupil to dilate. The most common concentration used in practice is 1%.

**Tropicamide**

Tropicamide is a parasympatholytic drug that is commonly used prior to examination of the fundus. It has a rapid onset of action (~ 15 minutes) and short duration of action (6–12 hours). Tropicamide is a very weak cycloplegic. Topical administration of this drug in dogs will not significantly affect intraocular pressure (IOP); however, in young cats, IOP can significantly increase to above the normal range. Tropicamide is available as a 0.5% or 1% concentration, the latter being the most common in practice.

**TEAR STIMULANTS AND LUBRICATING DRUGS**

Tear stimulants, lacrimogenic agents, and artificial tear supplements (lacrimumimetic agents) are needed in cases of tear deficiency and poor tear quality. Keratoconjunctivitis sicca in dogs is a common disease encountered in practice that usually requires life-long therapy. However, until tear deficiencies are addressed, lubricating solutions or ointments will be necessary to lubricate and protect the cornea.

**Cyclosporine**

Topical cyclosporine has been shown to be an effective treatment for canine KCS. Increased lacrimation is seen in normal and most deficient dogs after application of cyclosporine, but not in cats. Twice-daily applications are recommended, and life-long treatment may be required for most canine KCS patients. It is imperative that cyclosporine be given the morning of the recheck Schirmer Tear Test appointment to adequately evaluate response to treatment. Optimmune, 0.2% cyclosporine ointment, is the only licensed veterinary product for canine KCS. Although it may take 2–3 months for onset of action, documentation of drug failure should be done prior to trying off-label (compounded) preparations.
Topical cyclosporine is not recommended for cases of feline KCS and especially cases that are secondary to feline herpesvirus infection.

Topical cyclosporine has also shown beneficial effects toward other immune-mediated or inflammatory corneal diseases. As a precaution, handling of cyclosporine should be done with gloves, as it is an immunosuppressive drug.

**Tacrolimus**

Tacrolimus decreases T-cell activation and acts on different receptors than cyclosporine to increase lacrimation. Compounded products of 0.02–0.03% in oil or aqueous base must be used, as there are no commercially available products. This drug is an alternative to topical cyclosporine, as 50% of canine KCS cases that were unresponsive to cyclosporine increased their Schirmer Tear Test by 5 mm/min after administration of tacrolimus. As a potential link to cancer has been associated with the topical use of tacrolimus, recommendations are as follows: prescription of this medication in patients that are nonresponsive to cyclosporine, use of gloves when manipulating the drug, and avoid contact with children.

**Artificial Tear Supplements**

Artificial tear supplements are an important adjunct therapy for tear deficiencies. There are a multitude of artificial tears, eye gels and ointments on the market, and each have properties that can be advantageous for certain patients.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency of administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterinary products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optixcare</td>
<td>1 drop BID–TID</td>
<td>Water and carbomer</td>
</tr>
<tr>
<td>I-Drop Vet</td>
<td>1 drop BID–TID</td>
<td>Hyaluronic acid (0.15%)</td>
</tr>
<tr>
<td>Viscosity agents in human products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyvinyl alcohol 1.4–3%</td>
<td>1 drop TID–QID</td>
<td>Very watery</td>
</tr>
<tr>
<td>Carboxy/hydroxypropyl/methylcellulose</td>
<td>1 drop TID–QID</td>
<td>Differing combinations with polyvinyl alcohol or dextran</td>
</tr>
<tr>
<td>White petroleum</td>
<td>½-cm strip BID–TID</td>
<td>Many have no preservatives</td>
</tr>
</tbody>
</table>

**REFERENCES**

Vision - “What Does My Patient See?”
Chantale L. Pinard, DVM, MSc, DACVO
This conference will address the following questions: what do our patients see? Can they see the colors of the rainbow? See TV? Is the vision of cats better than dogs? These are all good questions that generate discussions with our pet owners. This conference will also explore the factors influencing our patients’ quality of vision. In addition, eye diseases that affect vision will be discussed.

VISION
In order to ‘see,’ there are three structures (eyeball, nerve conduction, and visual cortex) that are required to work in an optimal way to communicate information and produce an image. To begin “to see,” the waveforms of light are refracted by the cornea and the lens before reaching the retina. Light photons then stimulate photoreceptors, cones, and rods and cause a photochemical reaction. This reaction creates a cascade of nerve impulses that move through the different layers of the retina (the photoreceptor is similar to an antenna receiving information, while the ganglion cell is analogous to an optical fiber). The information then goes to ganglion cells and travels along their axons which form the optic nerve. Once the information is contained in the optic nerve, it passes through the chiasm, optic tracts and radiation to be finally interpreted by the visual cortex.

TYPES OF VISION
The composition of the retinal cell is species-specific. For example, in the dog and cat, there are less ganglion cells (fiber optic) but more rods (night vision reception antenna) than in most birds. The reason for this difference is the respective daily behavior of each species. The majority of birds, with the exception of owls, are diurnal animals that may have a very colorful plumage. Consequently, they mostly have cones, and cone:ganglion cell ratio is almost 1:1. This gives them the ability to see colours during the day and a visual acuity above others in order to see seeds (chicken, turkey) or prey in flight (falcon). In the dog and cat, the ratio of ganglion cell to photoreceptor is higher (less detail), the majority of the photoreceptors are rods (best night vision), and they possess a tapetum (to reflect light and thus improve night vision). In addition, the tapetum of the cat is more developed than that of the dog... so this is why our cats are more agile at night!

Colour Vision
Dogs and cats have cones, but the number is much lower than that of humans and most birds. Our patients have dichromatic vision; therefore, they can see two types of color compared to humans who can perceive three types. In dogs, the 2 types of cones stimulated by light photons are blue-violet (blue) and yellow-green (yellow). Blue-green and red appear as a shade of gray (partial color blindness to red and green). However, dogs can perceive more shades of gray than humans. In cats, the types of cones that have been identified are also yellow-green and blue. As aforementioned, compared to birds and humans, the canine and feline retina does not contain as many cones, and this also impacts the intensity of colour seen (the perceived color intensity is lower).

Photopic Vision
Day vision is due to stimulation of the cones by light photons. With respect to the position of the tapetum within the globe (dorsal retina), the dorsally located tapetum receives light emanating from the soil/floor (dark light), and the non-tapetum receives light from the sky (more bright light). The absence of cone function causes day blindness (hemeralopia); this condition is autosomal recessive in the Alaskan malamute.
**Scotopic Vision**
Night vision is very developed in dogs and cats, as their retina is composed primarily of rods. In our patients, the rods are densely populated in the visual streak, and this region is analogous to the macula of humans.

In addition, night vision is more developed in dogs and cats as compared to humans, because of the tapetum. The tapetum reflects light a second time to capture more light photons. The tapetum increases the vision of our patients when lights are low. As previously mentioned, the cat has a robust tapetum. It is estimated that the cat’s tapetum may reflect 130 times more light than the human eye, and it can also increase the wavelength of the light. In addition, the feline tapetum may lighten the appearance of the evening or night sky and increase the contrast between objects and the sky’s background. It is for this reason that the minimum threshold of light to see in cats is about 6 times lower than that of humans! With regard to dogs, the minimum threshold of light is higher than cats, but it is less than that of humans. In summary, cats have a better night vision than dogs, and dogs’ night vision is superior to that of humans!

**Motion Vision**
The rods are also responsible for the detection of movement. Thus, our patients have greater vision than us humans, because they have more rods! The last “type of vision” that our patients lose before complete blindness is motion vision. It is for this reason that many owners will notice that Fido can still see the squirrel run in the yard but has difficulty in perceiving a stationary object.

**Flicker Vision**
The vision of dogs and cats is different from that of humans, because the frequency of light stimuli to which the perception of flicker occurs in response to a feeling of continuous light is faster in our patients. In other words, the latent period of light stimulation and response is shorter for our patients. Scientific studies have shown that dogs are able to detect dancing lights at higher frequency than man. Old 60-Hz television models will quickly flash individual images for our dogs, while the new 120-Hz televisions will produce a continuous image.

**Accommodation**
The capacity of the eye to change its refractive power to see objects at various distances is accomplished by the contraction and relaxation of the ciliary muscle, resulting in changing the shape of the lens. This ability is measured in terms of diopters, the refraction power of a lens. Dogs have a low capacity of accommodation, because it does not exceed 2–3 diopters. This means that objects located 33–50 cm from the eyes form a clear image on the retina, whereas closer objects could be blurry. Cats have an accommodative power of 4–11 diopters. Primates may be able to accommodate to 40 diopters.

**Visual Acuity**
Visual acuity can be assessed with the help of Snellen fractions. The numerator of the Snellen fraction represents the distance at which the subject must be to decrypt a letter, and the denominator represents the distance to move a topic with the acuity of 1. For example, acuity of 20/20 means that the person placed at 20 ft can read a line of letters that it could read 20 ft, because visual acuity is equal to 1. Another explanation is that “normal human acuity” is a person at 20 ft can read the line designated 20/20 on the chart. Our dogs have a Snellen fraction of 20/65–20/85; a dog must be at 20 ft to read a letter that a human with 20/20 vision would be able to read at 65 or 85 ft. Cats have less visual acuity, as their Snellen fraction is 20/100.
ABNORMAL VISION

Ametropia
Ametropia is a refraction error where the focusing of light by the eye is erroneous and leads to an unfocused image on the retina; this in turn will reduce visual acuity. Hyperopia and myopia are types of ametropia.

<table>
<thead>
<tr>
<th>Hyperopia</th>
<th>Myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refraction error</td>
<td>Ocular globe is too short and image is focused behind the retina</td>
</tr>
<tr>
<td>Vision</td>
<td>Farsighted</td>
</tr>
<tr>
<td>Breeds at risk</td>
<td>Australian Shepherd</td>
</tr>
<tr>
<td></td>
<td>Alaskan Malamute</td>
</tr>
<tr>
<td></td>
<td>English Springer Spaniel</td>
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Convergent Strabismus and Nystagmus in Cats
This condition is especially seen in cats that are imperfect albinos (Siamese Himalayan and Burmese). Melanin is deficient in the retinal pigment epithelium, and there is an incorrect orientation of the axonal projections of the eye to the brain. There is also an increase in the number of optical fibres decussating in the optic chiasm of the temporal (lateral) retina. Such anomalies create abnormal retinopathic projections to the visual cortex and lateral occipital lobe. The central visual fiber routing error results in a reduction in visual acuity and the lack of binocular vision. Strabismus is noted to 3–6 months of age. In addition, nystagmus is strongly present in cats with convergent squint. Most cats with this anomaly compensate early on in life and can enjoy life like any other cat.

Blindness
The majority of causes of blindness occur at the level of the ocular globe. Significant opacity of the cornea, lens and media chambers can block information before it stimulates the retina. Retinal lesions may also block information and result in blindness. In addition, the optic nerve, optic chiasm and the optic tract must be intact to prevent blindness. Finally, the cortical function of the visual cortex (occipital lobe) must be present to ‘see.’

Dogs and cats, however, can ‘see’ with their noses, ears, and paws (vibrations in the ground) and thus deceiving most of us and making us believe that they are more visual than they are in fact! A test of maze with obstacles is one of the best tests to assess vision - but, once again, do not be fooled by very intelligent dogs that follow your voice or cats that jump on a chair while possessing a serious retinal atrophy!

EVALUATION OF VISION
During history-taking, several questions can help discern a visual deficit.
1. What behaviour has led to the suspicion of vision problems?
   a. Partial versus complete
   b. Right side versus left side
   c. Stationary versus motion
   d. Farsighted versus nearsighted
2. What environment is the behaviour seen?
   a. Bright versus dim
b. New environment versus home

3. How long has this behaviour been apparent?
   a. Acute versus chronic

4. Any medications: oral, topical?
   a. Ivermectin, Baytril

5. Any improvements with medication?

6. Any changes in personality?
   a. Suggesting cortical involvement
   b. Seizure versus behavioural stereotype

7. Any systemic signs?
   a. PU/PD, polyphagia

**Neuro-Ophthalmic Exam**
1. Dazzle reflex (subcortical CN II & VII)
2. Pupillary light reflexes (subcortical CN II & III)
3. Menace response (cortical involvement CN II & VII)
4. Maze test (dim-light and bright-light environments)
5. Cliff test (walking off a table)
6. Cotton ball test (drop cotton ball)
7. Visual placing test (approaching a table)

**Ocular Examination**
1. Corneal opacity
2. Anterior chamber cloudiness
3. Lens opacity
4. Vitreal cloudiness
5. Retinal disease

**Electroretinogram**
This test determines the normal, reduced or absent function of the retina and is performed by a veterinary ophthalmologist. This test is quantitative, not qualitative. An ERG can also detect differences between rod and cone function.

**Genetic Blood Tests**
There exist several blood tests identifying the presence of retinal disease causing blindness in a variety of dog breeds. The recommended company is OptiGen (www.optigen.com). It is worth noting that the owner receives the information and not the veterinarian.
Algorithm for Evaluating Loss of Sight

DISEASES AFFECTING VISION

Decreased Vision (Visual Deficits)
Partial or total opacity of the cornea can create visual deficits. Examples include pigmentary keratitis, chronic superficial keratitis, eosinophilic keratitis, conjunctival graft, or corneal scar.

A decrease in peripheral vision occurs in the beginning of glaucoma. Glaucoma can also produce intermittent peaks of high intraocular pressure with temporary vision loss before blindness becomes permanent.

Visual deficits and blindness can also occur with cataracts, depending on location and maturity.

A reduction in the field of vision can also be seen with a partial retinal detachment or retinopathy, as only a portion of the retina is affected.

It is important to note that a decrease in vision is difficult to discern for many pet owners, because our patients can easily adapt to visual deficits, especially if only one eye is affected!

Acute Blindness
There are several causes of acute blindness.
### Retinopathy

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th>Toxicties</th>
<th>Retinal detachment</th>
<th>Optic neuritis</th>
<th>CNS diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden acquired retinal degeneration (SARDS)</td>
<td>Ivermectin (dog)</td>
<td>Uveitis</td>
<td>Granulomatous meningencephalitis (GME)</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Immune-mediated retinitis (IMR)</td>
<td>Baytril (cat)</td>
<td>Systemic hypertension Spontaneous (Shih Tzu) Postsurgical complications (intraocular surgery)</td>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>

### Progressive Blindness

Certain nutritional deficiencies, including taurine and vitamin E, can lead to progressive blindness. Genetic retinal diseases associated with progressive blindness include dysplasia and degeneration in some breeds. Retinal dysplasia can be seen as rosettes, retinal folds, or geographic retinal detachment(s) and occur as a congenital form of retinopathy. Retinal degeneration mainly involves rods but can progress to involve cones. This night blindness can present as an early onset of blindness in some breeds (3 months to 3 years) and in other breeds, the blindness is late onset (1–5 years).

### The Future...

Retinal transplantation, stem-cell therapy, gene therapy, and artificial retinal prosthesis could be on the horizon for our patients. It is our responsibility to push the boundaries to combat blindness for our beloved pets.

### References

Mare Machinery: A Video Presentation Followed by a Q&A Session - Applied Anatomy of the Reproductive Tract of Mares
Robert Löfstedt, BVSc, MS, DACT
Department of Health Management, Atlantic Veterinary College University of Prince Edward Island, Charlottetown, PE, Canada
This is a modified script of the video by the same name.

There is no logical starting point when one discusses genital anatomy and its significance is arbitrarily, so let’s just start from the back and move forward.

The Clitoris
The clitoris is an interesting structure in mares, so much bigger and ostensibly, more significant than it may be in other animals. To start with, ask yourself when you last saw a clitoris in a cow or a bitch or a ewe. You probably haven’t or you can remember. Perhaps I am academically obsessed with this but I assure you that in other animals, they are invisible or very, very small in comparison to the mare’s clitoris.

So, why this interest in the clitoris? Well, if you are involved in the import or export of mares into Canada or if you happen to be unfortunate enough to find yourself involved in an outbreak of Contagious Equine Metritis (CEM) the clitoris will interest you. If you practice in the US or know anything about shipping semen from the US, you will know about the impact of CEM on the horse breeding industry; it counts in millions of dollars. The bacterium that causes CEM (an early embryonic loss syndrome) is the point of interest here. It is *Taylorella equigenitalis*; a bacterium that enjoys the microaerophilic environment in the small sinuses located in the dorsal part of the clitoris. There are three of these sinuses in the dorsal clitoral fossa; with tiny openings that are often filled with smegma; a perfect place for *Taylorella equigenitalis*. You should know where these sinuses are. Also note that the openings to the sinuses are so small that you will need to order special swabs to culture their contents.

There was a time when surgical removal of the clitoris was used as a method of controlling CEM but thankfully, it was found that *Taylorella equigenitalis* can live in other parts of the reproductive tract so this barbaric practice was stopped. Now, for the sake of this discussion, that’s probably enough on the clitoris.

The Vulva Lips...
Let’s move cranially, taking a look at the vulva lips. The vulva lips are normally well apposed and almost vertical in mares with good conformation, hanging together like the folds of a heavy curtain. This apposition prevents contaminated air from the perineum from being sucked into the reproductive tract as the abdominal pressure changes during breathing. If the vulva lips tilt forward, the folds of the “curtain” tend to hang open and a condition known as ‘wind sucking’ ensues. The same thing happens if the vulva lips have been damaged during foaling or have become scarred or distorted; the vulva seal compromised. Every veterinary student has been told that this is a cause of infertility in mares and some even remember it. Students have also been told that one uses the so-called “Caslicks” operation to treat this condition; closing up the dorsal two thirds of the vulva lips to prevent wind sucking. There are two kinds of “wind sucking” by the way; one and the back of the horse and one at the front. This one is at the back, not the one associated with cribbing!

Dr Edward Albert Caslick from Bourbon Kentucky published on the effect of vulva conformation in the Cornell Vet in 1937 and has achieved immortality as a result. Some say that we have selected for mares with poor conformation because of Dr Caslick’s paper but in the same breath, remind us that we are selecting for athletic ability in horses above all else so fertility should take a back seat. The truth probably lies somewhere in between.
In general we say that more than 70% of the length of the vulvar lips should hang below the floor of the pelvis so that they do not tilt forward and hang open. When that is not the case, we used Dr. Caslick’s operation to close up the dorsal two thirds of the vulva opening.

..AND THE VAGINA
Progressing cranially in the vagina, one finds a fold of vaginal mucosa just cranial to the urethral opening. This is a remnant of the hymen. It is circumferential and together with the vulva lips, serves as a seal between the outside world and the uterus. For that reason, it is also called the vestibule-vaginal seal.

One in a while, one will come across a persistent hymen in a mare vagina. I once used to believe that persistent hymens were very rare in mares but over the years, I have encountered enough of them to warn students and colleagues to look out for them, especially before natural breeding. A ripped hymen and blood on the penis of a million dollar stallion is not a good way to start your day. On one occasion I found myself with frozen-thawed semen in hand, at three o’clock in the morning, with a maiden mare and her persistent hymen; not a good situation.

Complete, imperforate hymens are not as common as those with one or more perforations or those that are simple bands across the cranial part of the vestibule. But even those remnants should be broken down before natural breeding or foaling.

The vestibule is, by the way, that part of the vagina between the vulva lips and the external urethral orifice. Fortunately for all female mammals with full bladders, the hymen is situated just cranial to the urethral opening.

Occasionally, the remnant of the hymenal fold provides substantial resistance when one passes a speculum into the vagina; so much so, that one cannot insert the speculum. Thoughts of transluminal adhesions and imperforate hymens go through your mind but a quick gloved hand examination reveals that this is nothing more than the hymenal fold. Usually, once the seal has been ‘broken’, the speculum can be passed into the vagina easily.

One last word on the hymen in mares: persistent hymens in maiden mares are different to those seen in heifers. In heifers, there is a massive accumulation of cervical mucus and metestral hemorrhage cranial to the hymen. This does not occur in mares because there is very little cervical gland secretion during estrus and certainly, no metestral hemorrhage.

THE AMAZING URETHRA
Before we leave the caudal part of the vagina, I should mention the amazing urethra in mares. It is as distensible as the amazing equine cervix, something we will discuss presently. If a urolith a few centimeters in diameter is present in the bladder, the urethra can often be dilated sufficiently so that a hand can be passed through it to retrieve the urolith. This can be done with the mare standing and tranquilized, over the period of time that it takes to discuss the local hockey scores and the progress of the children at school.

Also, there is no suburethral diverticulum in mares as there is in cows, so passing a urinary catheter into the bladder is very simple indeed.

THE CRANIAL VAGINA...
We are now in the cranial vagina. If you put a gloved hand in there you will feel the cervix just in front of you. Now, if you pointed to the left or right, just caudal to the cervix and were able to penetrate the wall of the vagina with your finger, you would enter the peritoneal cavity itself. This is the route we take when we perform an ovariotomy. Each ovary in turn is inserted into the loop of a chain ecrcaseur and removed per vagina. This is very useful technique; no general anesthesia and very few complications.
thanks to this convenient anatomical feature. There is however, a dark side to this feature as well. It comes at the time of breeding and foaling.

During natural breeding, the large penis of an over exuberant stallion can tear and penetrate the cranial vagina. The penis emerges, giving one the impression that the stallion has just ruptured a hymen or injured his penis. But soon afterwards, intestinal loops appear at the vulva lips and you know that something is awfully wrong. If you are lucky, the mare may survive but usually she dies. It is for this reason that over-penetration of the penis is prevented during routine natural breeding through the use of a so-called “breeding roll.” This rolling pin-like device is placed above the stallion’s penis during copulation.

In maiden mares especially, second stage foaling is particularly rapid and with this, comes the potential for tearing and destruction of the tract. If a foal is in foot-nape posture, its forelimbs can also penetrate the cranial vagina, with the same terrible result as occurs after a breeding accident. That is one reason that you should insist on a per vagina examination after foaling. I recall doing a routine per vagina examination, only to find that I was examining the left kidney and large colon. That mare lived because we were ahead of the game but if you arrive at the stable and those intestines are lying in the straw bedding, chances of a favorable outcome are worse than dismal.

...AND THE CERVIX
The equine cervix is a truly dynamic structure. Unlike the cervix of a cow, it changes substantially throughout the estrous cycle. But even during the luteal phase when it is relatively firm and organized, one can insert a finger into the cervical canal together with a device such as a catheter, culturette or biopsy punch. Try the same thing in a cow and you will see the difference! In mares, the cervix is so distensible that with some patience and gentle dilation, a five month old fetus can be withdrawn from the uterus. I know that because I have done it myself.

During diestrus, the cervix can be palpated per rectum but not easily in all cases. I should also add that the equine cervix cannot be grasped and picked up as is done in cows for during retraction, artificial insemination or embryo collection. This is because of the presence of a tense meso-cervix that suspends it within the pelvis. The meso-cervix is just the caudal part of the mesometrium. We will talk about the mesometrium later.

In early pregnancy, cervical tone increases dramatically so as soon as 15 days after conception, clear evidence of probable pregnancy can be detected. I say “probable” because this is not a guarantee that the mare was ever pregnant or that pregnancy continued after it was recognized by the uterus several days earlier. However, the difference between the cervixes of non-pregnant and pregnancy mares is remarkable. The change in cervical tone occurs before there is an obvious increase in tone in the uterus, yet this is seldom mentioned in texts on equine reproduction.

The equine cervix has longitudinal folds, not transverse ridges like those in cattle, so unless the cervix has been damaged, passing any device into the uterus is usually a simple exercise. In older mares however, the uterus can become so heavy and dependent that the cervical canal may be downward, making the passage of instruments a slightly more difficult task than otherwise.

At parturition, the mare’s cervix will dilate within a matter of minutes which is also very different to the cow. From the end of first stage when vaginal dilation begins to the time that the amnion appears at the vulva lips may be a matter of 10 to 20 minutes in mares. Compare this several hours in the cow. Of course, mares have the advantage of having larger vaginas as well, so this helps to speed up that process too. Have you ever thought just how different a mare’s vagina is from that of a cow? Try putting your hand in a cow’s vagina and you will see this immediately; quite remarkable considering that they both dilate to about the same diameter during the birth of their fetuses! But then again, the cow’s vagina was designed to accommodate the rather skinny bovine penis, very different to that of a stallion.
**Into the Uterus...**

OK, let’s move along to the uterus. The equine uterus has a long body, about as long as each of the uterine horns and each horn is about as long as one of your hands. This is unlike the situation in cows where there is a very short body and the uterus is comprised mainly of its horns. This has a couple of practical implications, one being that the uterine body in mares is usually accessed for flushing for embryo collection, not the uterine horns. No attempt is made to catheterize and flush each uterine horn independently, as is done in cows. Another implication is that the uterine anatomy of mares makes it more likely that transverse delivery will occur than in cows. This is because the equine fetus can develop across the uterus with its head and forelimbs in one horn and hind limbs in the other, with its torso easily accommodated in the uterine body. With their short uterine bodies, this is less likely to occur in cows. But fortunately, transverse presentation is not common in either species.

One thing to remember about the equine uterus is that it is firmly and horizontally suspended in the abdomen by relatively taught mesometrial ligaments on either side. This means that it is a more stable structure than the uterus of a cow, arguably making uterine torsion less likely in cows. I would not be too dogmatic in that argument but one thing is for sure; the uterus of a mare is too tightly suspended in the pelvis to retract it like one does during transrectal palpation in a cow. This is just as well because as I mentioned earlier on, the cervix cannot be grasped for retraction either. And one other thing, there isn’t even a substantial inter-cornual ligament in mares; something we also use during retraction in cows. But all of this really does not signify increased difficulty in transrectal palpation of the equine tract. On the contrary, the equine uterus is so well suspended by the mesometrium and is so predictable in its position within the pelvis that mares are certainly as easy to examine per rectum as cattle; perhaps even easier. One can stand ten yards from a mare and know pretty much the position and orientation of her uterus. In cattle, the mesometrium is so flaccid that this is just not possible.

I should remind you that uterine tone does not increase significantly during estrus, as is the case in cattle. Certainly, you can’t tell if a mare is close to ovulation by palpating uterine tone the way you can in cows.

**...And the Mesometrium That Supports It**

The mesometrium has already crept into this discussion once or twice, mainly from a point of view of its tense nature and the way it stabilizes the uterus and cervix. But remind yourself that the uterine artery runs through the mesometrium as well. We used to call this the middle uterine artery but its name has been changed to simply, the uterine artery; on the basis that there are no other uterine arteries.....which is not really the case. It is however, the main artery supplying the uterus on either side. Just a quick reminder: unlike the situation in cows you can’t feel fremitus in that vessel during pregnancy and it has no value in diagnosing pregnancy in mares. But to veterinarians, the vessel in mares is important in another way; it is occasionally damaged during foaling.

It is not clear how the uterine artery is damaged during foaling but it seems logical to suggest that the artery is pinched between the fetus and shaft of the ilium, causing it to rupture. This usually results in the formation of a hematoma within the mesometrium. In a few awful cases, the mesometrium tears and the mare dies of exsanguination. Some years ago it was suggested that ruptures of the uterine artery were due to copper deficiency but this is hard to swallow because breeders usually hang on to these mares and they often go through many subsequent pregnancies, completely unscathed. So I suspect this is an anatomical quirk and little else. Also, most brood mares are very well fed so nutritional deficiencies are unlikely.

**The Ovaries...**

Now let’s turn our attention to the ovaries. They are bean-shaped and three or four times larger than bovine ovaries, even during anestrus. They are usually about 5 x 3.5 x 3 cm in size in cycling mares but
can be considerably larger when large follicles are developing within them. In anestrous mares the ovaries are much smaller than when they are cycling.

One thing that makes an equine ovary so different from the ovaries of all other domestic animals is that ovulations do not occur though the surface of the ovaries. This is because a thick fibrous tunica; the so-called tunica albuginea, surrounds the entire ovary but for one small area, the ovulation fossa. The ovulation fossa sits in the center of the small curvature of the bean shaped ovary, right where a bean seed would be attached to its pod. And that is the only site on the ovary through which a mare can ovulate. Translated, this also means that no part of a corpus luteum can be felt or seen on the surface of the ovary. One can see and feel corpora lutea on the surface of the ovaries in all domestic animals but not in horses. But does this have any significance in practice? Absolutely!

One can easily tell if a cow is having estrous cycles after calving simply by palpating the crown of a corpus luteum on one of her ovaries. In mares this is impossible; you can palpate till you are blue in the face and you not be able to tell if a mare has begun to have estrous cycles at the start of the breeding season. That is why ultrasound is so important on an equine stud farm. In the old days it was far more laborious to ascertain if a mare was cycling. Now it is simply a matter of looking at her ovaries with ultrasound. If you see a corpus luteum, the mare can stay at the stud farm to be bred.

We are still in the ovaries, so I have to mention the totally unique follicle size and growth pattern of equine follicles. This is sort of half anatomy-half physiology but it definitely bears talking about in this context. In ruminants there are waves of follicle growth where mature follicles appear and regress all the way through the estrous cycle. One can see them in the ovaries on ultrasound, growing and regressing, growing and regressing throughout the cycle. This has great significance in the manipulation of bovine estrous cycles because there is always a follicle or two waiting in the wings to ovulate if one destroys the CL and brings a cow into heat. But this is just not the case in mares; well most mares that is, because mares usually only have a single follicle wave during the estrous cycle. From a bunch of small background follicles, a single star is born about 9 or 10 days before ovulation occurs. It is the chosen one, rising above all others and suppressing them with inhibin on its selfish mission to ovulation. The presence or absence of a corpus luteum will not affect the growth of the follicle, so (with few exceptions, notably Thoroughbreds) the bovine notion of short cycling by prostaglandin treatment has no place in equine stud practice. Thoroughbreds often have more than one follicle wave during each estrous cycle.

So now we have a nice big follicle, just about to ovulate; massive by comparison with that of the cow, not 16 to 22 mm in diameter but 35, 45 or even 55 mm. One can feel the follicle through the tunica albuginea and to some degree it tells us the mare is that ovulation is due. However, it is the appearance of the endometrium on ultrasound that gives us the assurance we need; not the follicle itself. In fact, large follicles do not always ovulate. It is the startling edema pattern on ultrasonography of the uterus that gives the game away because significant edema almost always means that ovulation is imminent.

...And Ovulation

Then ovulation occurs but as we have already said, mares don’t ovulate through the surface of their ovaries; only through the ovulation fossa. How then does the follicle move towards the fossa so that ovulation is possible? It doesn’t. Even though mares have large ovaries, their follicles are so large that a small part of the periphery of the preovulatory follicle comes to lie against the ovulation fossa. Quite simply, that part of the follicle is unsupported, so it ruptures and the oocyte is released into the black void beyond the ovary. I say this, not to be dramatic but to emphasize something that is nothing short of a miracle; the capture of the oocyte by the infundibulum of the oviduct, a virtual catcher’s glove, hovering close by. The edge of the infundibulum is attached to the ovary but looking at the space between the entrance to the fallopian tube and ovulation fossa, it still amazes me that oocytes are deposited into the oviduct so consistently. In humans, it is thought that the fimbriae (the “frilly” collar of
the infundibulum) sweep the ovulation fossa actively and guide the oocyte into the oviduct. In horses we really have no idea.

Nevertheless, the oocyte gets across safely in almost every case.

**THE UTERINE TUBE, OVIDUCT... OR IS THAT THE FALLOPIAN TUBE?**

I need to digress here for a moment; you may notice that I refer to the uterine tubes as either oviducts or fallopian tubes. In my opinion, a rather senseless name change has occurred in veterinary medicine. The new name for these structures is “uterine tubes”. The name “oviduct” actually means something to me but “uterine tube” is something that can be confused with the tubular structure of the uterus itself. In humans, the term fallopian tube is often used and in thousands of refereed journals one still finds the term oviduct, so I may use either of those terms in this presentation, rather than uterine tubes.

The infundibulum (< Latin for “funnel”) has a highly convoluted surface with numerous deep crevices and ridges. One cannot see these on casual inspection but they become evident when one floats the uterine tube in water. The oocyte is captured within these crevices then it moves down into the ampulla through the beating effect of millions of cilia that line the infundibulum and ampulla. The name “ampulla” is derived from the Latin word for “small flask” because it is a relatively thick part of the oviduct, certainly thicker that the next section, the isthmus, which leads into the uterus. Incidentally the word isthmus is derived from the Latin for a “narrow neck of land” an appropriate name for this skinny entrance into the uterus.

**THE UTJ**

For one final bit of applied anatomy let’s take a look at the junction between the oviduct and uterus; the uterotubal junction or UTJ. Perhaps you are aware of the worst possible construction of this junction; that is in the human. The opening between the uterus and fallopian tube is large enough to insert birth control devices into the tube, large enough to allow retrograde flow during menstruation causing endometriosis and of course, large enough to allow infectious organism to move into the peritoneal cavity causing periovarian inflammation. The cow comes a close second and it is not uncommon to find a large number of cows in slaughter plants where the ovary and its adnexa are wrapped up in fibrous adhesions. None of this occurs in mares. Search through a heap of specimens and you will probably not find a single periovarian adhesion; thanks to the design of the uterotubal junction in mares. It protrudes out into the uterine lumen and when pressure is applied to it from within the lumen, it closes, acting as a one-way valve, preventing fluid from entering the oviduct. It is surprising that sperm even manage to enter the oviduct.

**AFTER OVULATION**

After ovulation, an oocyte only spends a short time, perhaps hours or even minutes in the infundibulum and ampulla, moving down the fallopian tube rapidly to the isthmus where it is fertilized and will stay for several days. Usually sperm have been in that area of the tube for some time, even days, just waiting to fertilize an oocyte. The sperm can afford to be patient because the isthmus is about the best place for a sperm to be. The sperm become bound to the epithelium of the isthmus and drink and sustenance abound. While they wait there, the sperm undergo capacitation in preparation for fertilization. You should bear this in mind if ever have cooled semen in a container and are wondering if you should inseminate immediately or wait 24 hours. A mare’s isthmus can keep sperm alive for longer than five days but the very best transport container would be lucky to manage half of that. So always inseminate mares immediately with everything in the container.

The oocyte then embryo spends about five days in the oviduct before it enters the uterus. So it is foolish to attempt to collect an embryo from the uterus before five days have elapsed since ovulation.
Even on day 6, some embryos may be missed, so day 7 after ovulation is considered to be an optimal time to collect embryos in mares.

Finally, now that we are on the topic of embryo collection, remember to thank the mare for sorting out the live and dead embryos for you after you flush them from the uterus. Well in truth of course, there is usually only be one embryo because superovulation is a bit of a challenge in mares, but if there were more than one embryo, all would most likely be fertilized. This is because the equine oviduct is a special in another way; it only allows embryos and not oocytes to enter the uterus. This is because it is only embryos, not oocytes that produce prostaglandin E; a special passport for uterine entry in mares. It is only in mares that fertilized and non-fertilized oocytes are separated in this manner. All the other animals allow non-fertilized oocytes to enter the uterus together with embryos.

We could go on to talk more about the practical anatomy of equine pregnancies, placentation and fetal development; all fascinating subjects. But time does not allow it. Nevertheless, if you have any questions about these things or other matters pertaining to equine reproduction, please feel free to contact me at the e-mail address seen at the end of this presentation.

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From Follicle to Foal: A Video Presentation Followed by a Q&A Session (Basic and Essential Steps in Breeding Mares)
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This is a modified script of the video by the same name.
Hello and welcome to this presentation on breeding, pregnancy diagnosis and foaling.
Here are all the essentials you need to know about getting a mare pregnant. Time won’t allow us to go all the way through pregnancy but we will cover all the essentials and leave pregnancy and foaling to the mare herself.

FIRST DETERMINING IF A MARE IS CYCLING...
Now, because mares are generally in a state of anestrus during winter, the first thing you have to do of course is to make sure that your mare has started to have estrous cycles. Perhaps obviously; no estrous cycles equals no pregnancy.

It would be great if mares showed overt signs of estrus like, say cattle where cows have a mucous discharge during estrus and allow themselves to be mounted and have a hemorrhagic discharge when they go out of heat. Or like dogs, where there’s vulva swelling and a hemorrhagic discharge during proestrus. It would be a cinch to know if your mare is having estrous cycles. But, alas that is not so. Despite what you may hear from some horse owners like: “She’s winkin and pissin’ up a storm Doc, she’s gotta be in heat” or “I know, I can tell when my mare is in heat”… human beings are pretty damn useless when it comes to estrous detection in mares.

To tell that a mare has begun to have estrous cycles, you really need to do one of several things.

LOOK FOR A CL
The easiest thing by far, is to simply ultrasound those ovaries and look for a corpus luteum, which in mares is usually very easy to see. They are far easier to recognize than in cows. Corpora lutea can look like this at where the echogenicity is pretty homogeneous or they can look like a little hematoma with anechogenic cavities and fibrin strands running through them.

If you do see a corpus luteum, the mare must be having estrous cycles because there is evidence of a recent ovulation; and ovulation at regular intervals is the very definition of cyclicity.

If you are not sure if what you are seeing is a CL, you can always collect a serum sample and measure the concentration of progesterone.

.. BUT NOT JUST SIGNS OF ESTRUS
If, on the other hand you see something like this, send the mare home and tell the owners to give you a call in a couple of weeks because this is the typical appearance of a mare “in transition”, that is in transition between anestrus and cyclicity. During transition, there are large numbers of smallish follicles and no dominant follicle getting ready to ovulate. These mares are a pain in the neck because they can stay like this for months while you repeatedly try to convince the owner that it is too early to breed her. It is even more difficult to persuade the owner if they tell you that the mare shows signs of heat every time she passes by a gelding or stallion, because this is what they’ll do. Their mares will be in and out of behavioral estrus for weeks or even months before one of those follicles eventually becomes dominant and she ovulates. From then on, you are in business; she cycles normally, 15 days out in six days in, until late in the fall.

But what if you don’t have ultrasound? How do you know that the mare is cycling and there is a corpus luteum somewhere in the ovaries?
**BEING OUT OF HEAT IS MORE IMPORTANT THAN JUST SHOWING ESTRUS**

Well you could find a stallion and tease your mare until she comes into heat. But that of course presumes that you know how to tease a mare properly, that you have plenty of help and that you have the time do this every day until you know that she is out of transition and is having normal estrous cycles. But remember, you have to be a little cautious when you tease these mares because a mare in transition will wink and squat for the stallion and she will do this for days on end, sometimes weeks. The trouble is; she is not yet cycling. That is exactly what the owner saw when he said she was standing to be bred and looked like he was cycling. He was wrong. This mare is not going to ovulate and if you breed her, don’t expect her to become pregnant. Again, this is the state we call transition.

It is only when the mare goes out of heat and rejects the stallion that you know she has started to cycle. Let me put that a little differently. When she is cycling and she is restrained in a set of stock or behind a stable wall and the stallion approaches, she’ll wink and squat and definitely not kick for about 5 to 7 days. Then she’ll go out of heat because she is forming a corpus luteum and because of progesterone she becomes an absolute witch for another 15 days or so, squealing and kicking out at the stallion if he comes anywhere near her. When this behavioural pattern repeats itself, you know you’re in business. So you can see… teasing is quite a chore. I know this all too well from the days before we had ultrasound.

**DON’T TRY THIS**

Alternatively you could do something really simple. You could just throw the mare and stallion into a paddock and wait till next year for a foal. That is, if the stallion knows what paddock breeding is. If he doesn’t, he will probably get his genitals kicked in the first 10 minutes. I generally don’t recommend this.

**THE FERTILITY GODS MAY BE ON YOUR SIDE**

Or perhaps the fertility gods gave you the whole thing on a platter; in other words, a mare that just had her foal and ovulated at foal heat about 9 days later. Now she’s going to keep on cycling, even if it’s early in the season. You lucky devil!

**YOU COULD JUST WAIT**

If you don’t do too much of this, you may choose to just wait; wait until late May or even June when almost every mare in the Northern hemisphere is cycling normally. You may even have done a couple of progesterone assays to make sure you were on track. But bear in mind that if you wait and wait and wait, your foal is going to be born pretty late the next year. Maybe that is just fine and it often is, but if your foal is to be sold as a weanling or yearling, you want it to look as big and robust as possible in the sale barn. For that, you have to breed your mare as early as possible in the season.

**THE EASY WAY OUT**

OK I suppose you could also take the easiest way out and just send her and her foal off to a stud farm and let someone else do the job for you. Perhaps you don’t mind the boarding fees, maybe you don’t mind the risk of trucking and if there’s a foal, the risk of injury to the foal. Maybe you don’t even mind the risk of her getting some sort of disease at the stud farm. Mind you, if you felt that way, you probably wouldn’t be sitting here listening to this.

**WHAT WE DO…MOSTLY BUT NOT ALWAYS**

In general, on our stud farms, once we are sure a mare has begun to cycle, we carry on ultrasounding her until we see something exciting in her ovaries. Something exciting means a follicle greater than 35 mm in diameter and the appearance of edema in the uterine cross section. Then we collect semen from the stallion and inseminate her. Or we breed her to semen that has been shipped in from elsewhere.
After that we confirm ovulation and if she has not ovulated, we re-inseminate her. Fourteen or 15 days later, we examine her pregnancy.

But all this takes place on a stud farm and if you were running a stud farm, you would probably not be listening to this. It also presumes that you know your way around ultrasound and you have the experience and equipment to collect and evaluate semen.

**The Absolute Easiest Way To Get A Mare Pregnant**

Except for the wild stallion and his band of mares on the plains of Wyoming it’s about as simple as it gets. You can always dress things up a bit depending on your experience and equipment but right now I only want to get a solid core across to you.

Remember, no matter what approach you use, you still have to make sure that your mare is cycling before you can proceed. If she has been under lights since November the previous year, you may be looking at a cycling mare even when the crocuses are blooming but if she is like most other barren mares, it will be long afterwards. So lights can be very useful. They don’t eliminate transition of course, but they do make transition happen a couple of months earlier than usual, so you can cut down on the frustration factor at the start of the breeding season. And most of that frustration (as I said earlier) is trying to convince an owner that his mare is *not cycling* despite the fact that gives off all the cues that is doing so. In other words, just she’s winkin, blinking and pissin’ up a storm, don’t mean she’s cycling.

So let’s say you know for sure that your mare is having estrous cycles. What next?

**Make Plans To Breed Her**

Now you take the bull by the horns (or....the mare by the tail) and tell her exactly when you want her to ovulate because that is when you want to breed her. You want to walk up to her on that day (not on a Saturday or Sunday of course and not on Tuesday the 11th because that’s when you come back from Boston). No, it will be on Wednesday the 12th, because that it suits you best.

The first thing you have to do is to take over the controls to this mare’s ovaries. You have to stop the growth of her follicles and bring everything to a halt. It doesn’t matter where she is in her cycle, it is always the same treatment. By the way, if you have another mare you would like to breed, you can do the same to her...or another five or six. They can be at any stage of their estrous cycles when you start and you can breed them all on Wednesday the 12th.

**First, Control Follicle Growth**

If we can stop the secretion of follicle stimulating hormone secretion, that’s FSH, we can bring follicle growth to a screaming halt and put the ovaries to sleep. Then, after a while, we can take off the brakes, let her go back onto autopilot and let Mother Nature regulate the growth of here follicles. You see, most animals have very predictable rates of follicle growth and mares are no exception, so when we take off the brakes off FSH, its secretion increases and the ovaries wake up. Follicles start to grow and because their growth rate almost as precise as a Swiss clock, we know pretty much when they will be ready to ovulate. Then, when the follicle is mature, we give it a swift hormonal kick to make sure that ovulation occurs exactly on time. Then we breed her. And essentially, that’s all there is to it.

**Estradiol Is Where It’s At**

So what can you use to suppress FSH? Actually, you have a lot of choices but only one or two that are practical. A lot of hormones can suppress FSH secretion but the cheapest and most practical choice is estradiol; just plain old estradiol; not ECP, not estradiol benzoate or estradiol anything-oate. You must use plain old, simple, unconjugated estradiol. If you try anything else, this won’t work.

Now before you even try to remember this, just think why estradiol is one of your choices. Let’s use some metaphors. If you were a follicle and had grown fat and ready to ovulate thanks to follicle
stimulating hormone, you would probably to say: “Thanks FSH, you’ve been so good to me, but I don’t need you anymore. You may go now.” Indeed, understandably, as cruel as it seems, you would now suppress FSH, the hand that has just been feeding you. You actually suppress FSH with the payload of estradiol you are carrying in that rotund body of yours. Estradiol reaches the brain, puts the squeeze on GnRH and in turn, FSH. Ok, so I simplified it a bit but in essence all of that is true; with estradiol in hand, you have a powerful tool to control follicle development in any animal. In turn, you can also control its estrous cycle.

So let’s control that estrous.

**NO, IT’S NOT SORE**

Because estradiol has a fairly short half-life in circulation we have to give it every day to our mare for ten days. We give it via intramuscular injection. Now, you first response might be: “Geez isn’t she going to hate that?” The short answer is “No...most mares couldn’t care less. The owner just feeds her munchies and injects about three ml into the neck muscle. You second response may be: “Well why not use a long acting form of estradiol so you don’t have to jab her all the time?” Well, the answer to that is that when we take the brakes off FSH secretion, we want to take them off immediately, not grrrraduually, so we get a snappy, predictable response to treatment. If you use conjugated estrogens like estradiol cypionate or benzoate, you won’t get the results you expect because the conjugates are metabolized slowly. That’s why we use simple unconjugated estradiol in oil.

OK so let me see if I can predict your last question: “Why ten days?” The answer to that is that you can’t suppress follicle growth overnight. Some of the follicles in those ovaries are quite large so we have to keep on trucking until they regress in size completely. We also keep going so the smaller ones don’t make a run for it after we have suppressed the large follicles. Remember that you are not examining the ovaries during treatment do you don’t know what is going on. You don’t have to. Interestingly, some follicles may already be so big when we start treatment that we can’t suppress them and they go ahead and ovulate during treatment. But don’t worry about them; we’ll deal with that later. It’s not a big problem anyway.

Now, after ten days of treatment, all the remaining follicles in all the ovaries in all the mares treated this way will be no larger than about 2 cm in diameter. And that is baseline for a mare. If you treat one mare this way, she will be like that, if you treat 100, they will be the same. Again, it doesn’t matter where they were in their estrous cycles when you started treatment, as long as they were having estrous cycles. So you can see that this is not only a great way of handling one mare, it is a terrific tool for synchronizing estrous cycles in mares. If you have six mares to inseminate, you can inseminate them on the same day. If you want to transfer an embryo from one to another on the sixth day after ovulation, synchronizing their estrous cycles is a breeze.

**SOMETHING I HAVE BEEN KEEPING FROM YOU**

Now one thing I haven’t told you about yet is that we usually add progesterone to the estradiol we use. This is why the treatment is usually known as P&E; progesterone and estradiol. Actually progesterone is probably not all that important because it has very little effect on FSH and follicle growth but it can help to prevent ovulations during treatment and it will certainly stop your mare from become the “loose lady on the block” during all that estradiol treatment. Anyway, suffice to say; we end up using a combination of estradiol and progesterone for this exercise; 10mg of estradiol and 150 mg of progesterone intramuscularly every day. That ends up being a 3 ml injection.

**YOU DON’T HAVE TO MAKE IT IN YOUR KITCHEN**

Now, you don’t have to cook this up in your kitchen because many compounding pharmacies will make it up for you at very low cost. I have listed them at the end of this script. In fact, after all is said and
done, your client will probably be paying less than $100.00 for every hormone treatment included in the exercise.

SUPPRESSING FOLLICLES
So let’s see what happens during treatment. In this cartoon, treatment is taking place in four mares that are all being treated at the same time. Your mare could be any one of them, at any stage of her estrous cycle when you start the treatment; it doesn’t matter. See how the sizes of the follicles decrease as treatment progresses. That of course, is because you are suppressing FSH.

One of the follicles ovulates during treatment but we are not going to let that worry us. Suppression of any other follicles in this mare will be just as good as in the other mares. But, just to make sure that the corpus luteum formed here doesn’t complicate matters later on, we treat this mare with prostaglandin at the end of P&E treatment. In fact, we do that to all the mares we are treating with P&E because this whole exercise is blind; we don’t know if any mare has ovulated during treatment, we just use prostaglandin at the end of treatment in case one of them has ovulated. Your client is doing the injections and you are not examining the mare at all.

Just one word of caution here; if you are going to allow an owner to inject prostaglandins, you have to give them the 101 on safety because there are plenty of asthmatic out there and occasionally some mare owners are pregnant.

THE AUTOPILOT TAKES OVER
Now is when the autopilot takes over.

After the end of P&E treatment, you have taken the brakes off FSH secretion and Mother Nature now tells those follicles how fast or slow to grow. And as I said, it almost like a Swiss clock, the follicle growth rate is so predictable. So here, on day 8 after the brakes came off, there will be a large follicle somewhere in all the mares, just waiting to ovulate.

THE KICK IN THE PANTS
Now for the hormonal kick in the pants that seals the deal and makes that follicle ovulate on cue. That “kick in the pants” could be a GnRH analog that is going to release luteinizing hormone and cause ovulation or it could also be LH itself. But because equine LH is difficult to get and very expensive, we can use something that has pretty much the same effect as LH itself; good old hCG, that is, human chorionic gonadotropin. You could also use the GnRH analog deslorelin and your results would be pretty much the same but don’t use the native GnRH you use in cattle, it will not release enough LH to make a mare ovulate.

So, on day eight after the end of P&E treatment you will give your mare deslorelin or 2,500 iu of hCG (or thereabouts) and you will also make sure the semen is on its way from Whereversville. You will need it the next day. In fact, you could have phoned those people long ago because you knew weeks in advance as to when your mare was going to ovulate.

Now, it just so happens that most stud farms collect their stallions on Monday, Wednesday and Friday, so your breeding on Wednesday the 12th fits in just fine. You planned it so day eight after P&E was a Tuesday and day nine is Wednesday the 12th. They’ll collect the semen that morning and ship it out to you the same day.

THE SEMEN ARRIVES!
You’ll fetch your semen from the bus station or the airport, drive back to the stable and inseminate the mare. No warming up of the semen, no special treatment, no sleight of hand. Just bandage her tail, wash her up, put on a glove and some lube and insert an index finger slowly through her cervix. Follow that with a pipette to just beyond your finger tip and expel the semen slowly. Pull back and you’re done.
It is very simple indeed, nothing like inseminating a cow. In fact, many owners inseminate their own mares.

OK, now that you've bred the mare, you could of course check to see if she has ovulated. But you don't really have to. Remember, all of this has been a blind exercise, without you ever having looked at the ovaries, except perhaps for making sure that she was cycling.

**What Would You See Now (If You Wanted To)?**

But if you just couldn't contain your curiosity, you would see, in almost every case, that she had ovulated late at night on day nine after the end of P&E treatment, or early on day 10.

After using P&E for more than 25 years, it never ceases to amaze me how predictable ovulation can be. Now that's not to say that you won't get occasional failures. You do, and sometimes it is difficult to explain why. Sometimes I suspect the mare was not cycling properly when treatment began, or perhaps it was the owners fault, missing an injection or injecting the wrong volume. On occasion, it can also be because the P&E has been left in a cold barn and the steroids have crystallized out of solution. In more than 95% of cases however, P&E works very well.

Now, if you happen to be the inquisitive type and you ultrasound your mare and notice that ovulation has not occurred by day 10, don't panic or order more semen because sperm can usually last for a long time in the tract; for three to five days or even longer. The chance of conception will still be excellent even if ovulation is a delayed for a couple of days.

**Right, Now What?**

If you still want to do this with as little input as possible, you could cross your fingers, just stand back for about 11 months and wait for the mare’s udder to start swelling. But usually, your client will be itching to know if the mare is pregnant. You will be too.

If the mare is pregnant, you are going to have to treat her like a pregnant mare, vaccinating her against Rhinopneumonitis throughout pregnancy and feeding her accordingly as well. If want to know if the fetus if a filly or a colt but you will have to wait until about 60 days to do that. Most people could not be bothered with sexing but in some practices it can be quite common.

But wait; there is something pretty important that we have to discuss it before this show is over. And that is, the possibility of twins. You see, there is about a 15 to 20% chance that your mare will have twin ovulations and a twin pregnancy, especially if she is a Thoroughbred cross or if it is summertime or if she’s had twins before. You are, I think, walking on thin ice if you leave it all to Mother Nature from now on because as you probably know, twins are a significant cause of abortion in mares and very few twins go to term and become viable foals.

It is true that most twins are eliminated in the first half of gestation, so you don’t really have a 15 to 20% chance of a twin abortion; just less than half of that. But it is still significant, and something that you don’t want hanging over you for the next 11 months.

**So How Do You Diagnose Twins?**

The problem is, that by the time you can do a pregnancy diagnosis by palpation alone, say about 28 to 30 days, it is far too late to do anything about twins. If you try to eliminate one, you will almost certainly terminate the whole pregnancy.

The only time you can tackle twin pregnancies safely, is early on, about 14 to 16 days after ovulation. This is because the uterus is still moving the embryos back and forth throughout the uterus, making sure the endometrium has recognized pregnancy. But at about 16 days, this movement comes stops and the embryos become fixed against the endometrium. Once that happens, your chance of crushing one embryo without harming the other, diminish quickly. That’s because most of these embryos become fixed next to one another and they can’t be separated easily to crush one safely. Even
if they have become fixed far from one another, the amount of tissue destruction from crushing an embryo after 16 days is great enough to harm a co-twin some distance away. And that will be the end of that; all of your effort and cost for nothing.

So this is when you should consider calling in a colleague who has an ultrasound unit. Someone who has some experience dealing with twins. At 14 to 15 days after ovulation, after a careful search to make sure that only one embryo is at home, you can breathe easy. If there are twins, one embryos can be crushed safely and in almost 100% of cases, a singlet pregnancy will continue.

Just a warning here; over the years, it has become apparent to me that if a co-twin is missed, it will have been in the uterine body at the time of examination. Therefore it is essentially that the characteristic echogenicity of the lumen of the body be traced from the horns to the cervix and back again so no pregnancy is missed. In fact, this is important in any pregnancy diagnosis in a mare.

JUST BE AWARE OF THE PITFALLS
So yes, you could do the pregnancy diagnosis by palpation alone, but just be aware of the caveats. I would suggest however that you should try and get this diagnosis done by ultrasound before 16 days of gestation. There is too much at stake.

So, there we have it; from follicle to foal. Well not quite; there are still about 11 months to go before the foal is up and suckling and much more we could discuss. But that is for another time.

SOME SOURCES OF P&E
- Summit veterinary pharmacy Inc.
  Prescribe with confidence
  25 Furbacher Lane, Aurora, ON L4G 6W3
  Phone: 905-713-2040; Fax: 905-713-1095
  http://www.svpri.ca
- Compounding pharmacy of Manitoba
  106 Terracon Place
  Winnipeg, MB
  R2J 4G7
  Phone: 204-233-6590
  Toll Free: 1-855-623-0833
  Fax: 204-233-6655
- Ford’s family pharmacy and wellness centre
  544 St. George Blvd.
  Moncton, NB E1E 2B5
  Phone: 888-644-3673
  Fax: 506-853-0832
  Email: pford@fordrx.ca
  www.fordrx.com

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Cooled and Frozen Equine Semen
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The Growth of the Cooled-Shipped Semen Industry
Cooled transported semen has been used for at least 30 years to provide convenience, genetic improvement, excellent conception rates and safety in breeding. I can’t recall exactly when the cooled transported semen industry took off but it was perhaps about 1986, when Meg Plum created the embryonic form of Hamilton Thorne Biosciences. I recall clearly sitting down with Meg and her brilliant husband Diarmad Douglas-Hamilton. The surface we were working on was a plasma lightning coffee table designed by Diarmad, a plasma physicist; perhaps an indication of the innovation and brilliance of what was to come. On the back of a napkin, Diarmad was jotting down his concepts for the first Equitainer and his idea for an optimal cooling curve for sperm. In the last 27 years, that system has become the cornerstone of the North American cooled semen industry. Many other systems have followed of course, mostly disposable systems. Hamilton Thorne themselves have their own disposable system on the market.

One thing has driven the growth of the shipped cooled semen industry more than anything else is the often unpredictable fertility associated with frozen-cooled semen. Ask yourself if you see shipped cooled semen in wide use in the cattle industry; of course not. The reason for that is that frozen-thawed semen is usually highly fertile in cattle. In horses, we fall back on the usually reliable technique of shipping cooled semen. At least, this is certainly the case in North America when the frozen semen industry is not as well developed as it is in Europe.

Although the cooling curve of the Equitainers is better controlled than it is in the disposable units, all of these systems work pretty well in practice. It is just when the environmental temperature fluctuates significantly that some the disposable containers may show their limitations. Most systems can hold semen at temperatures of less than 15 degrees C for 30 to 60 hours at room temperature. However, Equitainers appear to be superior to others at low environmental temperatures. But, even with Equitainers, semen can be frozen rock hard if it is transported in the unheated baggage compartments of aircraft and buses.

Let’s take a look at this video of stallion collection and semen packaging. Afterwards, I will comment on philosophical changes that have occurred since I made it eight years ago.

Well, not a huge amount has changed. But there have been changes.

Dosage Rates for Cooled-Shipped Semen
My usual approach nowadays for dosage calculation is to use morphology together with motility to calculate the number of usable sperm. We often make a rather naïve presumption that the motile sperm are also morphologically normal, which of course, they are not. One sees this leap of faith in the use of both cooled and frozen semen.

It is logical to incorporate the percentage of normal sperm into the dosage calculation together with the percentage of progressively motile sperm. The question however, is how does one do this? When you examine sperm morphology, how can you know what proportion of the normal-looking sperm are motile. Similarly, how can one determine know what portion of the sperm with expanded midpieces, droplets and abaxial head attachments were swimming along just fine, fooling you into thinking they were “normal”? One cannot see many abnormalities in motile sperm.

For several years now I have multiplied the proportion of sperm with normal morphology with the proportion of sperm that have normal motility. This calculation presumes that the motile sperm have the same proportion of morphologically abnormal sperm as the general population. This is a pessimistic
view but a safe one; certainly safer that presuming that all the motile sperm have normal morphology. True, we end up with fewer insemination doses than otherwise but I feel safer this way. I normally refer to these doses as having a certain number of “usable sperm”. Many years ago Bill Pickett at Colorado State University showed that under ideal conditions, normal conception rates could be expected with about 100 million progressively motile spermatozoa. Others researchers have also shown that to be the case. However, ideal conditions seldom exist, so when are inseminating mares on our own stud farms, we have always used twice that number; 200 million progressive motile. Some colleagues still cling to much higher insemination doses; often 500 million live based on improved conception data with higher doses that also appeared at CSU at that time. But whether it was through conversations with Bill Pickett or from reading other data, I have consistently used the 200 million dose for 25 years or more. Our conception rates have always remained high, in one remarkable season on one stud, over 85% on first ovulations! Interestingly, for most of those years we did not incorporate morphology into that numbers so I have no idea of how many “usable sperm” we were actually inseminating!

As mentioned, many still use a minimum insemination dose of 500 million live and this figure is still widely published. However, in a recent review of the subject by Steve Brinsko, the use of lower doses than 500 million is supported. Unfortunately, a calculation of “usable sperm” is still not widely discussed.

Very low doses of sperm can be used if only small numbers of sperm are available (for example when sexed semen is used). In fact, doses as low as 5 to 10 million sperm can be used. But such small doses must be inseminated at the utero-tubule junction using endoscopy or special A.I. equipment to achieve reasonable conception rates.

Our standard dose for shipping semen is more than twice as high as the dose we use locally. As mentioned, we use 200 million locally. Translated, this means we ship about 500 million usable sperm, that is, the same number that many people use locally. Those who use 500 million sperm locally usually ship about 1 billion. Again, that number seems excessively high to me but whatever figure one uses, they generally suggest that we think we are losing about half of the sperm during transport. This is based on an unscientific and conservative assumption proposed by Hamilton Thorne in the early days of the Equitainer. It stated that one may stand to lose half of the usable sperm during transport. In truth, we may lose 50 percent, we may lose less but we may lose many more. It depends on the stallion and the extender. And that brings me to the next subject; the need to evaluate every stallion in a “storage trial” before using his semen.

One thing that we should all be aware of is the problem of stallions that do not “ship well.” On rare occasions, a shipment of cooled semen will arrive where there is either very poor motility or all the sperm appear to be dead. In the distant past we were too quick to blame the people shipping the semen. Perhaps the artificial vagina had been contaminated with detergent or perhaps they had cold shocked the semen. Had they even bothered to examine the semen after diluting it? True, these factors can be important, but now it has become clear that the semen of some stallions just doesn’t ship well. This may be because the sperm do not survive cooling well or it can be due to inherent incompatibility between the sperm and the extender. Strangely, it can also be because endogenous seminal plasma has a toxic effect on sperm during cooled storage. The cause of this is not known. Auto antigenicity has not been excluded but it is clear that when the seminal plasma is removed in these ejaculates and resuspended in extender, the motility and longevity of the sperm improves dramatically. One can use practically any extender for resuspending the sperm, but one extender that has performed very well for this purpose is the so-called Kenney’s extender modified with Tyrode’s solution, better known as KMT. Details of KMT extender can be found in the Texas A&M manual on Equine reproduction.
TESTING STALLIONS FOR THEIR ABILITY TO “SHIP WELL”

As mentioned, one should test stallions for their ability to “ship well” before using them. To do this, the semen can be diluted in a couple of common extenders for example, Kenney’s and INRA 96. Kenney’s extender can be used without antibiotics or with the addition of penicillin and amikacin. INRA96 usually contains penicillin, Gentocin and amphotericin B. After conducting my own studies on antibiotics and motility many years ago, I was convinced that sperm and many antibiotics did not make good bedfellows but many controlled trials have since shown that most antibiotics don’t in fact have a significant effect on sperm motility. There is one exception: polymixin B; it is definitely toxic to sperm.

Interestingly, we have not used antibiotics in our extenders for the better part of 30 years and our conception results with both local and shipped semen have been more than acceptable. Long ago I experience of two Warmblood stallions that consistently shed Pseudomonas and untyped Klebsiella and whose fertility was excellent in the absence of antibiotics in the years that I knew them. That was perhaps tempting fate but it was during the time that I was very cautious about using antibiotics in semen. I would probably not do the same thing today.

It has been said that when contagious equine metritis is a concern (caused by Taylorella equigenitalis) Clavumox and ticarcillin can be added to semen extenders but I am not sure that I would trust any antibiotic if I was using semen from a stallion that was suspected of shedding Taylorella!

BACK TO THE SHIPPING TRIAL

After dilution at a ratio of 1:2 to 1:3 for the shipping trial, the semen should be packed in an Equitainer at a total volume of between 120 to 170 ml so that the proper cooling curve is attained. Other containers can be used as well, according to their directions. Then, after keeping the container at room temperature for 24 hours, aliquots of the extended semen are placed on slides at 37 degrees C and tested for motility. If possible, the test period should be extended up to 72 hours so that weaknesses are given a chance to become apparent.

If the semen does not ship well in any extender, you may want to send it to someone who has a large centrifuge so that the sperm should be removed as soon as possible after collection. In that case, the extended ejaculate is centrifuged between 200 and 400 g for about 20 minutes (many different centrifugation protocols have been suggested) and the sperm pellets are collected and resuspended in an extender as alluded to earlier. If it appears as though it is neither and extender nor a semen plasma problem, one can try shipping the semen at about 15 degrees C, cooled to just below room temperature. One extender that has been shown to work reasonably well at this temperature is INRA 96.

Incidentally, I recently read that unused portions of INRA96 should not be frozen and reused, despite instructions from the manufacturers. If this is done, it has detrimental effects on sperm motility.

WHAT ABOUT EXTENSION RATIOS?

For many years we used extension ratios of between 1: 1 and 1: 6 (semen: extender), usually in the range of 1:2 to 1:3 with excellent first-ovulation conception results. Recent data suggest that sperm concentrations should be in the range of 25 to 50 million per ml after extension. Now, if one considers that typical sperm concentrations in an ejaculate are about 40 to 120 million/ml, a threefold dilution of an ejaculate containing 100 million sperm/ml would give a final concentration of about 30 million per ml. Therefore, depending on the concentration of the ejaculate, simple dilution ratios of 1:2 to 1:3 will probably deliver optimal concentrations of sperm.

THE INSEMINATION VOLUME

The ideal volume for the insemination dose has been juggled around for many years. At one time, it was shown that conception rates were no different if volumes varied between 0.5 and 60 ml as long as they
contained the required number of spermatozoa. Subsequent data suggested otherwise, showing that
doses higher that 50 ml were not advisable. After that, even more data showed that original data were
probably correct; volume did not seem to be important. So, in our practice we use volumes that range
anywhere from 25 to 35 ml but as I’ve just mentioned, this range could be even wider.

**TWO DOSES IN ONE SHIPMENT**
Occasionally you will receive two doses of semen per ovulation in one shipment. The question is: do you
inseminate it all at once, or inseminate the second dose 24 hours later, perhaps closer to ovulation.
Controlled trials have been done to determine which is best and in the minds of some, the jury is still
out on the subject...but not mine. Essentially we are comparing sperm longevity in an Equitainer or
something similar, to sperm longevity the female tract.

Insemination four or five days before ovulation often results in pregnancy but we know that
conception is unlikely if semen is inseminated after five days in a shipping container. Also, bear in mind
that special conditions exist in the ampullary-isthmic area of the fallopian tubes for the preservation of
sperm. The female tract is designed to harbour and protect sperm, in some species for several days, in
others for weeks or even months. With these facts in mind, I recommend inseminating all the available
sperm immediately upon arrival.

**IT’S TIME TO TALK ABOUT FROZEN SEMEN**
My experience with frozen equine semen got off to a rocky start about 17 years ago. A group of
Warmblood breeders on PEI decided to upgrade the value of their stock by breeding to a well-known
Stallion whose name still haunts me. For the sake of this discussion, I will call him THAT DAMN STALLION
(TDS). He is still alive and if you Google his name, this is what you will find:

*TDS also produced many talented jumper and hunter offspring including ______, ridden by ______
who competed as a speed horse for ______ in Gottenburg, Sweden and was her reserve horse for the
World Cup Finals in Paris in ______. TDS is the damsire of a number of popular approved stallions. TDS
descends primarily from British and Irish TBs who trace back to the foundation TBs used in European WB
breeding.*

Yes, he was quite the boy! And better still, his frozen semen was available through some sort of
special deal. It was all too good to be true. Of course it was.

We lined up 14 mares, 11 to be bred to TDS and three others, to be bred to three other stallions.
The three others became pregnant and the 11 we bred to TDS came up empty. My professional pride
took a nose dive and the 11 owners of the 11 mares were left aghast. How could this have happened
with such a prestigious and proven stallion? The fingers of accusation pointed directly at me. The
program came to a grinding halt and not another word was said. To try and exonerate myself was
impossible. So, with my tail between my legs, I took sabbatical leave in Europe, determined to learn
more about frozen semen in horses.

Now, many years later, I have forgotten most of those clients but I doubt if they have forgotten
me. However, should I ever encounter one, I have a prepackaged avalanche of explanation ready to
launch. And this is how it goes:

**FROZEN SEMEN 101**
First, most stallions don’t freeze well. Pregnancy rates range from 0 to more than 70% per cycle, but
first-cycle pregnancy rates are in the range of 25% to 40% for many stallions. In 2005 the French
National stud, when stallions are selected for their ability to freeze well, the first-cycle pregnancy rates
on about 2000 mares was 48%.

The important thing to bear in mind here is that the fertility of stallion semen in the frozen-thawed
state has little correlation with its fertility in the natural or cooled transported state; very little indeed.
Unfortunately, especially in North America, stallions are often marketed as though that is the case. Very few have substantial data as frozen sires and often semen is sold through wholesale merchants who do not keep data on its fertility. When the semen is used, little or no data returns to the stallion owner or processor on the fertility of the semen. It is only when a foal is born to frozen semen that some data accumulates. Owners are not required to report all breedings; therefore, failed breedings seldom become part of the record of on a frozen sire. It is only where semen processors conduct their own fertility trials before selling semen, that trustworthy data on the performance of frozen sires is available before the semen is purchased. This is becoming common in Europe but is comparatively rare in Canada and the US. Take for example, this inquiry from me to a large supplier of frozen semen in the US:

**Hi (The vendor’s name),**

I am interested in (The stallion’s name). Please can you answer the following questions in turn:

- Did you freeze him or was he frozen in France by someone else?
- What are you selling his doses for?
- Presumably no 15 day PD/ advanced PD or live foal suckled guarantees?
- How many straws are there for each dose?
- Is he packaged in 0.25 ml straws?
- Does he have a special thawing protocol?
- When did they/you first start freezing him?
- How many mares has he been bred to in total in each years?
- What was his fertility (first ovulation conception rate)?

Finally, the advert for his semen states that he is “Easy to breed.” What does that mean?

Cheers and thanks in advance.

-Rob

**THE REPLY:**

Hi Rob,

He is frozen in France. I don’t do any semen processing, I only sell it. I sell all of my frozen semen with no guarantee and no restrictions.

- I am selling (The stallion’s name) by the individual 0.5 ml straw at $1650 per straw, or by the four-straw dose for $6400.
- I am not sure when they began freezing him, but I have been aware of his frozen being available for a few years.
- I do not know how many mares they breed, but he is available via fresh cooled semen in Europe and frozen semen worldwide.
- He has a lot of foals, and the reputation of his semen quality is excellent. Both his supplier and the “word on the street” is that he has excellent frozen and an excellent first-cycle conception rate with frozen. I have not personally purchased his semen before, this will be my first order, but everything I have heard or read about his semen is that it is excellent.

Below is a quote from his owner, re: his semen quality:

“Our best guarantee of (The stallion’s name) fertility rate is the results in the different AI centers all over the world. You can ask many, many vets. All are OK to say that (The stallion’s name) is one of the most fertile stallions available on the market, with only 1 straw in deep AI on ovulation.”

All the best,

(The vendor’s name)
Assured? No, me neither.

**WHAT HAPPENS WHEN YOU FREEZE SEMEN?**
When you freeze semen, you put the sperm through all sorts of physical and chemical torture. Water leaves the cell and cryoprotectants (glycerol, ethylene glycol, methylformamide and others) are added to prevent the formation of large ice crystals, stabilize membranes and control osmotic damage. The sperm shrink as they cool and a multitude of chemical changes occur within them. The reverse happens when they are thawed. Yet, amazingly many sperm make it through this punishment. But not all species and not all individuals have sperm that freeze well. In general, most bull semen freeze well but mentioned, the ability of individual stallions to freeze well is highly variable. In a conversation with Dr H. Sieme of the national Hanoverian stud at about the time of my first foray into frozen semen, he told me that approximately 70 percent of the stallions he had worked with could not be frozen successfully. By that he meant that their post-thaw motility was less than 35%. I’ll discuss motility as an indication of fertility in a few moments.

**SO WHO WILL FREEZE WELL?**
The trouble is, it is impossible to tell which stallion will freeze well and which won’t. And importantly, you certainly cannot tell by looking at their fertility in the non-frozen state. As you will recall, I mentioned the figure of 35% post-thaw motility in my conversation with Dr Sieme. In point of fact, that figure means very little because post-thaw motility is very poorly correlated with post-thaw fertility. I found that out the hard way. The stallion I mentioned at the start of this section (TDS) had post-thaw motility of 60% or better. In my naïveté, I was very much encouraged; all I had to do was to get that semen in those mares at the right time and the right dose and I was on easy street. I could not have been more mistaken. As mentioned, not one of the mares we bred to him became pregnant.

Some research has correlated a particular aspect of motility to fertility, but the general consensus is that post-thaw motility is not a good predictor of fertility. This also holds true for other tests, such as amino acid uptake after thawing, Sephadex filtration tests, chromatin integrity, tetracycline staining and so on. Unfortunately, other than breeding, there is no test that is a good predictor of post-thaw fertility. The problem is, a huge amount of frozen semen from stallions is sold without assurance of fertility. As you have just seen, when vendors are asked about the fertility of their frozen semen, data are often anecdotal, spread over several seasons and are often based on very low numbers of mares. In North America, the sale of frozen semen based on first-cycle conception rates is a rarity.

**COMPARE HORSES AND CATTLE**
Compare the frozen semen situation in horses with that in cattle. In the cattle industry, only semen that is of proven fertility is sold to the breeder. It has usually been tested on several hundred virgin heifers and one of two standard packaging systems is used. In cattle there is a close-to-standard dose of sperm, standard freezing and thawing protocols are used and there is usually a standard site for insemination. Also, insemination is always very close to the time of ovulation and insemination is usually done by technicians with standardized training. Under these standardized conditions, minimum first-service conception rates of about 60% would be expected of most bulls that are sold as frozen sires. In cattle, insemination is done with a mind to improving milk production, conformation, feed conversion and so on. The last thing on the mind of the cattle breeder is the fertility of the semen in that liquid nitrogen tank. In the case of horses, it is the first thing.

**A NAÏVE ASSUMPTION**
In the equine frozen semen industry, frozen-thawed semen is commonly used as though it has been tested for fertility but that is a naïve assumption. No virgin heifers here and a complete lack of
standards! The semen could have been used on 7-year olds, 5-year olds, 13-year olds and so on. A mare could have had 3 foals, one difficult foaling and one abortion. One mare could have been bred at the onset of the breeding season, another in late summer. The semen could be packaged in 0.5ml straws, 5 ml “Macro tubes”, ampoules or even foil packages. Packaging could even be different from season to another. Semen could have been frozen in the fall (when it may be more fertile according to some) or in summertime. The recommended time of insemination relative to ovulation is variable, the frequency of insemination different, the dose is different, and the site insemination is different. Also, those handling the frozen-thawed semen do not have standardized training analogous to that of bovine AI technicians.

In essence therefore, the best methods for processing and using frozen equine semen have not yet been discovered. Also, it is often impossible to obtain reliable data on the actual fertility of frozen-thawed equine semen because it is used under such diverse conditions. Good fertility under some conditions may translate to poor fertility under other conditions.

**The Timing**

Let me tell you a little more about what people are actually doing in this convoluted mish-mash of possibilities. Some routinely inseminate every 24 hours during estrus until ovulation is confirmed. This carpet-bombing approach is fine if there is practically unlimited supply of frozen semen. For example, this is the case in the French national stud where each mare has a starting budget of 36 straws of semen. But it is not a great approach if you have to pay $1650 for a single straw or $6400 for a four straw dose. In those cases, mares can only be inseminated once, after the follicle has reached a critical size and hCG has been given; alternatively and perhaps more safely, within 6 to 12 after ovulation has occurred. The problem with inseminating mares before ovulation is that one can inseminate a mare and 48 hours can go by without ovulation, even if hCG has been given. This is not a happy situation when you have just used a $6400 dose of semen. Fresh-cooled semen will remain fertile for several days after insemination because frozen-thawed semen has such a short and variable lifespan, a 24 to 36 hour interval between insemination and ovulation is pushing the envelope. This is why I usually inseminate mares within 6 hours of ovulation; a simple task in most cases if P&E is used to set the time of ovulation. Unfortunately the use of P&E is prohibited in many countries where horses are also used as a food source.

**...And The Thawing**

After frozen semen is removed from the tank, expect to find an array of recommended thawing procedures. Straws may be thawed at 37 degrees C for 20 to 30 seconds or at 75 degrees for 7 seconds. Foil packages may be thawed in the hand and 5 ml “Macro tubes” with, at 50 degrees C for 40 seconds in the case. When one is in doubt, it is best to contact the processor for instructions.

**...And The Dose & Where You Put It**

So what about dose and deposition? The dose of frozen-thawed semen is very variable, just as it is with cooled transported semen. Sometimes it is 400 million progressive motile after thawing, sometimes half that. The dose could be contained in 4 straws, 10, 12 or more. To inseminate those, you will need a special AI catheter that is only inserted into the uterus once allowing many straws to be used without excessive contamination of the tract. These are commercially available. Sometimes very small doses of sperm are used, occasionally less than ten million, in small volumes. These are deposited at the uterotubal junction using endoscopy or special AI catheters. But those are unusual conditions, usually encountered in infertile stallions or when sex-separated semen is being used.

By the way, did you notice that I mentioned nothing about incorporating morphology in determining the dose of frozen-thawed sperm? As for cooled shipped semen, the subject of “usable” sperm is seldom mentioned.
**The Bottom Line**

OK, what does this all add up to?

First, frozen equine semen is an invaluable resource and a great tool for genetic improvement. However, you must do a reality check with mare owners when they first mention the use of frozen semen.

Although high conception rates are possible with frozen semen, it is commonly not very fertile. Therefore, veterinarians must warn owners about the potential pitfalls of using frozen equine semen. Owners must be encouraged to accumulate as much data as possible on the fertility of frozen sires before they part with their money. Also, when first attempts are successful, these should be tempered with reality. Small successes should not be magnified through optimism into unrealistic expectations.

Those who custom freeze equine semen are of course fully aware of this situation and some seek to improve it by gathering pregnancy data whenever possible. But frozen semen may only be used years after it is sold and it can travel far and wide, sometimes changing ownership before it is used. Therefore, fertility data remain elusive and a source of frustration for the industry. Apart from the eventual registration of foals from a sire, the link between his frozen semen and its fertility are usually tenuous.

As far as possible, semen processors should be encouraged to track the fertility of their frozen sires by charging for semen only when pregnancy in confirmed at 14 days after ovulation or only when foals are registered. This is currently the situation with cooled shipped semen. Obviously this will be unpopular with frozen semen vendors because it means delayed returns on investment. It will also mean that certain guideline be adhered to in the use of that semen. Unless this is done, mare owners are being asked to take unfair financial risks while stallion owners and semen processors are in effect, asking mare owners pay for the fertility trials of untested stallions. For the reputation and improvement of the industry, the status quo must change. Only after stallions have been proven as frozen sires, should latitude can be exercised in marketing their semen.

**References**

Diagnostic Ultrasonography in Bovine Reproduction
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Veterinary Biomedical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, SK, Canada

Take Home Message
- Use of ultrasonography in bovine practice began in 1980’s and is now routine practice.
- Detectable changes in the uterus and ovaries are predictive of the estrous cycle.
- Ultrasonography is particularly useful for early pregnancy diagnosis, assessing fetal health, and fetal sex diagnosis, twinning, diagnosing pathology and response to treatments.
- Ultrasonography is not associated with higher embryonic loss.
- Imaging the ovaries in cattle has led to an understanding of follicular and luteal dynamics in this and many other species, and to new protocols for ovarian synchronization, fixed-time artificial insemination, and superstimulation.
- Advances in 3-dimensional ultrasonography, Doppler imaging, ultrasound biomicroscopy, and computer-assisted analysis of ultrasound images will ultimately enable us to determine the precise stage of the estrous cycle based on a single examination, and the health status of individual follicles and their contained egg.

Introduction
Ultrasonography has become an important diagnostic tool and is gaining widespread popularity among bovine practitioners. Ultrasound imaging capabilities are also progressing rapidly, and the information accessed by visually examining the uterus and ovaries through the “ultrasound window” can no longer be regarded as ancillary to that of more traditional methods of examination, including transrectal palpation. Training and experience are required to be able to obtain and interpret ultrasound images, but ultrasonography is not inherently difficult to master. What may initially appear as incomprehensible gray smudges on a 2 dimensional image will soon be appreciated as a dynamic 3-dimensional organ - even to the novice. The following is a brief overview of the applications of ultrasound imaging in bovine practice, and some new and potentially powerful applications. The reader is also referred to other reviews on the applicability of ultrasonography in bovine practice (Ginther 1994; Rajmahendran et al. 1994; Guilbault et al. 1998; Hill et al. 1998; Quintela et al. 2012).

How Does Ultrasonography Work?
Current ultrasound instruments for use in cattle are portable, B-mode, real-time scanners which include a console and a transducer or “probe”. B-mode, or brightness modality refers to an image composed of a 2-dimensional display of dots of varying brightness. Real-time refers to a live or moving display of echoes recorded instantly and continuously, analogous to the continuous image production of a cinema. Piezoelectric crystals in ultrasound transducers vibrate at a characteristic ultrasonic frequency when electrically stimulated and cause alternate compression and rarefaction of tissue molecules that moves through the tissue in a wave.
The crystals in the transducer emit a thin (i.e., 2 mm) “curtain” of sound waves and, depending on the density and characteristics of the tissue, sound waves are either transmitted (nonechogenic) or reflected (echogenic). The transducer is connected to the console by a cable comprised of many wires connecting individual crystals to both a pulser and a receiver. Electrical stimulation is episodically turned on and off by the pulser to allow the crystals to vibrate and emit sound waves and then to “listen” for reflected sound waves (echo) which again cause the crystals to vibrate. The vibration caused by the echo is transduced back into electrical impulses that are sent to the receiver, are amplified, and converted to a moving real-time image on a television screen. Hence, this process is often referred to as pulse-echo diagnostic ultrasonography.

The proportion of sound waves reflected is represented on the ultrasound image by shades of gray varying from black to white. Fluid-filled structures (e.g., ovarian follicles, embryonic sac) are nonechogenic and produce a dark or black image. Tissues of increasing density (uterus, cervix, bone) have increasing echogenicity such that the image varies from dark gray to white. Accordingly, this process has also been referred to as gray-scale diagnostic ultrasonography. Analogous to the way in which a knife can be used to slice a loaf of bread, the ultrasound beam acoustically slices the tissue it passes through to provide a sectional image of its interior. Ultrasound waves do not propagate through bone or air and result in “shadow” or “reverberation” artifacts. Therefore, ultrasound gel is applied to create fluid contact between the transducer lens and the tissue of interest.

Of the 3 major types of ultrasound transducers, sector, convex-array and linear-array, the latter is used most commonly to image the reproductive organs. Linear-array transducers have a row of crystals embedded side-by-side along the length of the probe. Sequential stimulation along this array produces a rectangular image, the horizontal length of which corresponds with the length of the row of crystals (e.g., 5 cm). The minimum size of a structure that can be imaged (resolution) and the clarity of the image are a function of the resolving power of the transducer and the quality of the scanner. Higher frequency transducers (e.g., 5 or 7.5 MHz) provide greater resolution than low frequency transducers (e.g., 3.5 MHz). For example, a 3.5 MHz transducer can effectively image a structure (e.g., embryo) 6 mm in diameter, but a 5 MHz transducer can image a structure 2 mm in diameter. High resolution, however, is gained at the expense of penetrating ability. Great penetration is generally not needed during intrarectal use because the transducer is in close proximity to the reproductive organs; the tissues of interest are usually no farther than 6 cm from the transducer surface. A 5 or 7.5 MHz transducer is the instrument of choice for most reproductive examinations.

**IMAGING THE UTERUS**

Characteristic changes of the tubular genitalia visible by ultrasonography involve thickness of the uterine body, evidence of increased vascularity and edema, and accumulations of mucus (Figure 1; Pierson, Ginther 1987). The period of proestrus and estrous Days -4 to -1 (Day 0 = ovulation) is characterized by 1) increasing thickness of the uterine body, 2) accumulation of luminal fluid first in the uterus followed in succession by fluid in the cervix and vagina, and 3) minimal curl of the uterine horns. Conversely, diestrus, (Days 3–16) is characterized by minimal thickness, minimal luminal fluid, and maximal curl to the uterine horns (Figure 1). Heterogeneous endometrial echotexture (interspersed areas of dark and bright gray) is reflective of uterine edema and is associated with impending estrus and ovulation.
Figure 1. Changes in uterine luminal fluid (0, minimal; 3, maximal), degree of uterine horn curl (1, minimal; 4, maximal; A, B), and uterine echotexture (1, homogeneous; 3, heterogeneous) during the inter-ovulatory interval in heifers (n = 58)
Adapted from Pierson, Ginther 1987.

**IMAGING THE CONCEPTUS**

**Early Pregnancy Diagnosis**
There are numerous reports of the use of ultrasonography for evaluating pregnancy in cattle (Curran et al. 1986; Kastelic et al. 1991; Griffin et al. 1992; Mee et al. 1994; Romano et al. 2006; Quintela et al.)
2012). Early diagnosis of pregnancy is based on the detection of discrete, nonechogenic fluid pockets or lines within the uterine lumen, but must be subsequently confirmed by progressive elongation of the fluid pocket and detection of an embryo proper. The accuracy of early pregnancy diagnosis was not greater than a guess (50%) before Day 18 using a 5 MHz transducer, or before Day 16 using a 7.5 MHz transducer (Kastelic et al. 1991). The accuracy of early pregnancy diagnosis based on fluid alone approached 100% by Day 20 (Kastelic et al. 1991). Characteristics inconsistent with a diagnosis of pregnancy at Day 20 are signs of impending estrus and ovulation, including intrauterine fluid that accumulates on average 2 or 3 days earlier than that of pregnancy, intravaginal fluid, increasing uterine tone, estrus-like uterine echotexture, and a regressing corpus luteum. Confirmation of pregnancy may be made by detection of an embryonic heartbeat (~ 140 beats/min.) that is first detectable between 21–25 days (Table 1). After 26 days of gestation, overall accuracy of transrectal ultrasonography for pregnancy diagnosis was reported to be ≥ 95% (Quintela et al. 2012).

Regarding the expediency of the technique, results of one study (Galland et al. 1994) showed that an experienced operator can diagnose pregnancy and estimate fetal age (between 45 and 108 days) in an average of 16.1 seconds using ultrasonography, compared to 11.3 seconds for palpation. The authors concluded that use of ultrasound at ≥ 45 days of gestation may not increase the accuracy of diagnosis for an experienced palpator, but will for a less experienced one. More time was required to estimate fetal age in pregnancies between 65 and 85 days than those at either 45–60 days or 90–108 days (Galland et al. 1994). The requirement for more time during the middle stage coincides with a period of relatively subtle changes in the fetus compared to other stages.

**Embryo/Fetal Development**

During early pregnancy, the uterine horns in pregnant cattle become compartmentalized by segmental contraction of circular smooth muscle, and it was concluded that formation of several chambers is the reason the bovine embryonic vesicle cannot be imaged in toto (Kahn, 1989). During the first 2 months of gestation, detection of specific anatomical structures are helpful in estimating gestational age (e.g., embryo proper, heartbeat, amnion, eye, placentomes, ribs; Curran et al. 1986; Table 1). When the uterus is located cranial to the pelvic inlet, a false negative diagnosis is more likely to be given than when the uterus is within the pelvic cavity (Szenci et al. 1995). The bovine fetus can be imaged throughout gestation, but becomes too large to image in its entirety using a standard 5 MHz probe beyond about 70 days.

After about 2 months of gestation, measurement of the dimension of fetal structures is helpful in estimating the stage of gestation (e.g., length of long bones, diameter of the eye, brain case, stomach and abdomen; Kahn 1989). The regression coefficient of changes in fetal dimensions over time was > 0.9 for 24 of 26 fetal structures examined by transrectal ultrasonography from Day 60 onward (Kahn 1989). Transcutaneous ultrasonography in the lower right flank has been used as an alternative to the transrectal approach, but although specificity is high during early pregnancy, the sensitivity was low until 155 days of gestation (Hunnam et al. 2009). Using the right flank approach, fetal thoracic, abdominal, and umbilical diameters were useful indicators of gestational age between 73 to 190 days of gestation (Hunnam et al. 2009).
Table 1. First day of detection of ultrasonically identifiable characteristics of the bovine conceptus (Day 0 = ovulation)
From Curran et al. 1986.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean day</th>
<th>Range</th>
<th>Characteristic</th>
<th>Mean day</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo proper</td>
<td>20.3</td>
<td>19 to 24</td>
<td>Eye orbit</td>
<td>30.2</td>
<td>29 to 33</td>
</tr>
<tr>
<td>Heartbeat</td>
<td>20.9</td>
<td>19 to 24</td>
<td>Hindlimb buds</td>
<td>31.2</td>
<td>30 to 33</td>
</tr>
<tr>
<td>Allantois</td>
<td>23.2</td>
<td>22 to 25</td>
<td>Placentomes</td>
<td>35.2</td>
<td>33 to 38</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>29.1</td>
<td>26 to 33</td>
<td>Split hooves</td>
<td>44.6</td>
<td>42 to 49</td>
</tr>
<tr>
<td>Forelimb buds</td>
<td>29.1</td>
<td>28 to 31</td>
<td>Fetal movement</td>
<td>44.8</td>
<td>42 to 50</td>
</tr>
<tr>
<td>Amnion</td>
<td>29.5</td>
<td>28 to 33</td>
<td>Ribs</td>
<td>52.8</td>
<td>51 to 55</td>
</tr>
</tbody>
</table>

Embryonic Loss

Diagnosis of pregnancy can be made earlier by ultrasonography than by palpation, hence, more pregnancy losses (early embryonic death) will be detected. However, the technique per se does not appear to cause embryonic death (Ball, Logue 1994; Baxter, Ward 1997). Furthermore, the incidence of pregnancy loss (cows that aborted or returned to estrus before term) after ultrasound diagnosis was not different among cows that were first examined at 30, 40 or over 50 days of gestation (Baxter, Ward 1997). Similar rates of pregnancy loss have been reported among studies involving transrectal ultrasonographic diagnosis of pregnancy in cattle: 5.5% loss after ultrasound diagnosis on days 30 to 40 (Baxter, Ward 1997), 8.6% after diagnosis on days 26 to 58 (Szenci et al. 1998), and an estimated 10% after diagnosis on days 25 to 45 (Mee et al. 1994). By comparison, in a study of 10 dairy herds involving 4,208 pregnancies (Forar et al. 1996), pregnancy loss (return to estrus, observed abortion, follow-up examination) following transrectal palpation at day 45 (median; range 38 to 80) of pregnancy was 10.8% (range among herds, 7.6 to 13.0%). The nature of embryonic loss has also been investigated in cattle, and ultrasonographic characteristics have been described (Kastelic 1989; Baxter, Ward 1997). Results of these studies have dispelled the mistaken notion that uterine “resorption” is the common mode of eliminating the early conceptus. Results indicate that embryo/fetal fluids and tissues are retained until the ensuing estrus when they are expelled through the cervix, usually unnoticed. Signs of impending loss include cessation of the heartbeat, disorganization and detachment of membranes, and the presence of less intraluminal fluid than would be expected for the stage of gestation.

Twinning

The diagnosis of twins is of increasing importance in the dairy industry where milk production has been positively related to the incidence of multiple ovulation and twinning (Quintela et al. 2012). Twinning is associated with increased risk of pregnancy loss, freemartinism, and dystocia (Silva del Rio et al. 2009). Accurate diagnose of twins may be made only after the embryo proper becomes detectable. The entire length of both uterine horns must be scanned to ensure that an embryo is not missed, and care must be taken to ensure that a single embryo is not observed twice. Multiple fetuses were accurately diagnosed
between 49 and 55 days post-insemination in one study (Davis et al. 1993), and between 26 and 107 days post-insemination in another (Izaike et al. 1991).

**Fetal Sex Diagnosis**
Transrectal ultrasonography can be used to accurately diagnose the sex of the fetus in cattle based on identification of the genital tubercle (Curran et al. 1989) or the scrotum and mammary gland of the male and female fetus, respectively (Muller et al. 1986). Ultrasonographic location of the genital tubercle allows earlier identification of the sex of the fetus (Days 50 to 100) than detection of the scrotum or mammary glands (Days 73 to 120). The genital tubercle is that which develops into the penis in the male or the clitoris in the female, and is a very prominent structure both grossly and ultrasonographically. The genital tubercle starts out in an undifferentiated position between the hind limbs of the fetus and, beginning on about Day 45, gradually migrates to a position behind the umbilicus in the male or beneath the tail in the female by about Day 55. Under experimental conditions, the experienced operator was able to diagnose the sex of the fetus with 100% accuracy after Day 55 (Curran et al. 1989). Under farm conditions (Curran et al. 1991), an accurate diagnosis was made in 93 of the 97 dairy cows (96%) examined between approximately Days 50 and 100. When the certainty level at the time of diagnosis was high (95 to 99%), a correct diagnosis was made in 65 of 65 animals (100%). Diagnosis could not be made in 5% due to an inability to obtain an adequate view of the genital area in some of the older fetuses (Days 65 to 101). The optimal days for diagnosis were Days 55 to 64, and the time required to make a diagnosis averaged 1 minute 53 seconds (range, 16 seconds to 8 minutes). Others have reported similar accuracy; i.e., 84/85 (Beal et al. 1992), 200/213 (Lamb 2001).

**Imaging the Ovaries**
Nowhere have the effects of ultrasound imaging been more evident than in our understanding of ovarian physiology (reviewed in Adams et al. 2008; Figure 2). More studies have been published on ovulation, follicular- and luteal-dynamics in cattle than in all other species combined (Singh et al. 2003).

**Follicle Dynamics**
The majority of bovine estrous cycles (> 95%) are composed of either two or three follicular waves. A surge in circulating concentrations of FSH precedes emergence of each wave. A surge in circulating concentrations of LH precedes ovulation. The LH surge is preceded and succeeded by a period of high LH pulse frequency as a result of low circulating concentrations of progesterone (i.e., period of luteolysis and luteogenesis, respectively; Adams et al. 2008). Under the influence of progesterone (e.g., diestrus), dominant follicles of successive waves undergo atresia. The dominant follicle present at the onset of luteolysis becomes the ovulatory follicle, and emergence of the next wave is delayed until the day of the ensuing ovulation. The CL begins to regress earlier in 2-wave cycles (Day 16) than in 3-wave cycles (Day 19) resulting in a correspondingly shorter estrous cycle (19 to 20 d versus 22 to 23 d, respectively). Hence, the so-called 21-d estrous cycle of cattle exists only as an average between 2- and 3-wave cycles. In a recent study (Jaiswal et al. 2009), the wave pattern was repeatable within individuals, and duration of the estrous cycle was reflective of the wave pattern; i.e., 90% of cycles ≤ 21 days were 2-wave cycles and 80% ≥ 22 days were 3 wave cycles.
The Corpus Luteum
The reliability and accuracy of ultrasonography for detecting the CL, and the relationship between ultrasound image attributes and CL function have important implications in clinical settings for assessing normalcy and stage of the cycle. In a comparison between ultrasonographic detection vs. gross anatomic dissection, there was 83% agreement in inexperienced operators and 97% agreement in experienced operators (Ginther 1998). The growing CL was detected by Day 2 (Day 0 = ovulation) in > 95% of 80 estrous cycles, and the regressing CL could be detected on average, 1.4 days into the next estrous cycle (Ginther 1998). About 70% of normal corpora lutea have a central fluid-filled cavity during their development and the remainder are solid structures; the cavity becomes smaller and often disappears as the CL matures. Plasma progesterone concentrations are not different between CL with or without a central cavity, and the profile of luteal tissue area (minus area of a cavity if present) detected by ultrasound paralleled the profile of plasma progesterone concentration, with the exception that during luteolysis progesterone began to decrease 1–2 days before ultrasonographic regression was apparent (Kastelic et al. 1990). In addition, changes in ultrasound image attributes (exchotexure) of the CL are reflective of CL function (Singh et al. 1997)

Figure 2. Ovarian and hormonal dynamics during 2-wave and 3-wave estrous cycles in cattle
Dominant and subordinate follicles are indicated as open (viable) or shaded (atretic) circles. A surge in circulating concentrations of FSH (red line) precedes emergence of each wave. A surge in circulating concentrations of LH (yellow line) precedes ovulation. The LH surge is preceded and succeeded by a period of high LH pulse frequency as a result of low circulating concentrations of progesterone (i.e., period of luteolysis and luteogenesis, respectively; Adapted from Adams et al. 2008).
Ultrasound-Guided Techniques

Ultrasound-guided techniques (Fig. 3) have provided the opportunity to collect oocytes transvaginally for in vitro embryo production in mature and prepubertal cattle (Pieterse et al. 1988; Brogliatti et al. 1996). Repeated follicle aspiration attempts every 3 to 6 days for the first 16 days of the cycle were done without any apparent detrimental effects to subsequent fertility, and did not cause remarkable ovarian adhesions (Pieterse et al. 1991). Of 541 follicles ≥ 3 mm, an oocyte collection rate of 55% was reported in adult cattle. One can expect to obtain between 10 to 17 oocytes per animal (50% collection efficiency) after ovarian superstimulation (Dias et al. 2013). After biweekly follicular aspirations from cattle, an average of 2.1 embryos/week were produced from oocytes collected and fertilized in vitro, which is about 4 times greater than the number of embryos produced by traditional embryo transfer methods (Kruip et al. 1994). A transvaginal approach has also been developed for oocyte collection in prepubertal calves too small to accommodate intrarectal placement of the operator’s hand (Figure 3, Brogliatti et al. 1996). A 38% oocyte collection rate was achieved from 87 follicles ≥ 5 mm in 16-week old calves. Moreover, repeated ultrasound-guided transvaginal follicle aspiration in the calves did not alter subsequent ovarian function or pregnancy rate after puberty (Brown et al. 1996).
Figure 3. Transvaginal ultrasound-guided follicle aspiration in cows (above) and calves (below) for oocyte collection or ovarian synchronization (follicular ablation)

Follicular ablation by transvaginal ultrasound-guided aspiration of ovarian follicles has also become an effective tool for ovarian synchronization in cattle (Bergfelt et al. 1994; Baracaldo et al. 2000). In cattle, synchronous emergence of a new follicular wave was induced 1.5 days after ablation, and prostaglandin treatment 4 days after ablation resulted significantly better ovulation synchrony than prostaglandin alone (Bergfelt et al. 1994). The technique is also effective for wave synchronization prior to ovarian superstimulation (Bergfelt et al. 1997).

The transvaginal technique has also led to novel studies involving follicular fluid sampling (Ginther et al. 1997), local or intra-follicular injections (Kot et al. 1995), and gamete recovery and follicular transfer (Bergfelt et al. 1998) to better understand the effects and capacity of individual follicles of a wave and their oocytes. Although amniocentesis and allantocentesis are not frequently done in bovine practice, transvaginal amniocentesis has been used to determine if a specific gene was incorporated into the embryonic genome resulting in a transgenic embryo (Salaheddine, Garcia 1996). Transvaginal ultrasound-guided amniocentesis, using a 22-g needle on days 78–90, resulted in no pregnancy loss (n = 48), compared to surgical amniocentesis (after flank laparotomy) with an 18-g needle on days 120–169 (n = 2/23). Pregnancy loss may have been due to needle diameter, pregnancy stage or the technique.
itself, but transvaginal ultrasound-guided amniocentesis appears to be a safe method to collect samples from the pregnant uterus (Salaheddine, Garcia 1996).

**THREE-DIMENSIONAL ULTRASONOGRAPHY**

Conventional B-mode ultrasonography involves continuous visualization of two-dimensional “slices” of a tissue (e.g., ovary, uterus, fetus) and mental reconstruction of the tissue structure in the third dimension. This is a technically demanding procedure that has impeded exploitation of the full potential of this type of medical imaging. Advances in computing power and transducer design have now made three-dimensional (3D) imaging possible. A tremendous advantage of 3D imaging is that once the images are acquired and reconstructed, the image may be rotated in all different planes and evaluated without continued scanning. Further, the 3D data sets can be used to provide volumetric measurements and permit acoustic sectioning or “peeling” of layers, revealing both internal and external features.

**COMPUTER-ASSISTED IMAGE ANALYSIS**

An ultrasonographic image is composed of thousands of picture elements, or pixels, representing tissue interfaces with a reflectivity of ranging from black to white (256 shades of gray in a 8-bit gray-scale image). The human eye can perceive “smoothness” of an image, but can only distinguish between 18 to 20 shades of gray. The status of tissues can be assessed through the use of computer-assisted image analysis.

**Spot, Line and Region Analysis**

The simplest quantitative method to analyze the pixels comprising an ultrasound image is to select one or multiple small circular or polygonal areas of interest (Figure 4; reviewed in Singh et al. 2003). The computer can readily determine the precise values of all of the pixels (black = 0, white = 255) within the selected area and provide an average value (mean pixel value) and a standard deviation value (pixel heterogeneity; Singh et al. 1997, 1998). In line analysis, the amplitude of echoes located along the line may be depicted in a graph (Figure 4). The antrum-wall interface of the follicle can be detected easily by identifying a sequential rise in grey-scale values along the line. Using the antrum-wall interface as a reference point, pixel values along the line can be divided into three segments, thus allowing separate analyses of the peripheral antrum, follicle wall, and stroma (Singh et al. 1998).

Region analysis of a follicle involves overlaying a pixel-by-pixel “mesh” onto a selected area (Figure 5) for recording pixel values at the points of intersection and generating a 3-dimensional wire-frame model. A computer generated gray-scale or color “skin” can be placed over the framework to yield a topographical surface. The approach may develop into a diagnostic tool useful in clinical settings permitting instant visual assessment of attributes associated with follicle health.

**Figure 4. Computer-assisted image analysis of ultrasound images of the ovarian follicle**

The follicle wall from (a) is enlarged (b) to display the picture-elements (pixels) forming the ultrasound image. Spot-analysis of the antrum is performed by measuring pixel values within the area of each circle (A,B,C,D). Line-analysis of the follicle wall (b). The pixel value graph (c) was divided into 3 segments (peripheral antrum, follicle wall, stroma) to enable statistical regression analysis of each segment separately (modified from Singh et al. 1998).
Physiologic Correlates of Image Attributes

In an initial studies of high-resolution ultrasound images of bovine ovaries examined at specific phases of follicular wave development (Singh et al. 1997; 1998; Singh, Adams 2000), it was concluded that quantitative changes in the echotexture of ultrasound images occur concurrent with changes in functional and endocrine characteristics of ovarian follicles and CL. The thickness and vascularity of the follicle wall, and the functional status of the CL were reflected in ultrasound image attributes. Results of studies documenting a relationship between image attributes of ovarian follicles and competence of the contained oocyte to develop into an embryo (Salamone et al. 1999; Vassena et al. 2003) provide rationale for the use of ultrasound image analysis for identifying follicles that will produce competent oocytes. Similarly testicular echotexture has a positive linear regression with daily sperm production ($P < 0.002$) in bulls (Kastelic et al. 2001). Although the sensitivity of this technique is not yet sufficient for use in a diagnostic setting, the identification of statistically significant endpoints has formed the basis to improve the imaging technique.

Figure 5. Regional analysis of a single preovulatory follicle

A) Image of the follicle with follicle wall identified (black line). B) Wire-frame model of the pixel by pixel mesh created from the image of the follicle. C) Computer generated “skin” stretched over the wire-frame model. D) Height-shaded color algorithm added to the image to enhance visual appreciation and allow comparison of different zones with images of different follicles or images of the same follicle on different days.
With the objective of developing an image-based classification system that can automatically determine the stage of the estrous cycle based on a single day’s ultrasonographic examination of the ovaries, computer algorithms were tested using images of bovine ovaries known to be in either the early (metestrus), middle (diestrus), or late (proestrus) phase of the estrous cycle (Eramian et al. 2007). The classifiers performed with 86% to 100% accuracy and the results support the hypothesis that the phase of the cycle can be automatically and robustly determined from ultrasound-detected features based on a single day’s examination. This constitutes an important step in what may become a fully automated system. Segmentation of follicles ≥ 10 mm has been successful (nearly 100%; reviewed in Eramian et al. 2007). If future work can achieve a robust segmentation algorithm for the CL, the entire process could be fully automated.

**Vascular Imaging**

The Doppler effect is a result of relative compression or rarefaction of ultrasound sound waves from an approaching or departing source, respectively, and is the underlying reason for a change in acoustic pitch (frequency) from a moving sound source (blood flow towards or away from the transducer). Major changes in the microvasculature of the ovary occur during growth and regression of large follicles and the corpus luteum (Singh et al. 1997; Singh, Adams 2000; Acosta et al. 2004). Hence, important physiologic processes may also be studied by characterizing changes in vascular dynamics over time (e.g., velocity, resistance, volume). Three variations of the Doppler technique have been used to study vascular flow: 1) Spectral Doppler is used to display vascular flow over time in a waveform, 2) Color-flow
Doppler permits superimposition of information about vascular flow direction on the B-mode grey-scale image, and 3) Power-flow Doppler is used to superimpose low velocity vascular flow information (without directional information) on the B-mode grey-scale image.

Doppler studies have provided visual evidence for time-related changes in blood flow within the preovulatory follicle wall of cows in relation to LH surge (Acosta et al. 2004; Siddiqui, Ferreira 2010). Initial results indicate that a biphasic blood flow response to LH may occur in the bovine preovulatory follicle. An initial increase in blood flow was accompanied by serration of the follicular granulosa layer within 3 hr of LH treatment, and a second increase in blood flow was detected around 20 hr after LH (Siddiqui et al. 2010). Distinct changes in vascular flow patterns during luteogenesis, luteolysis and early pregnancy, and in response to GnRH, PGF, PGE, PGI, oxytocin and NOS have been reported in cattle (Acosta et al. 2004; Honnens et al. 2009; Siddiqui et al. 2009; Herzog et al. 2011; Brozos et al. 2012; Garcia-Ispirto et al. 2012). One of the problems with color-flow imaging is that artifacts resulting from random noise during ultrasonography may resemble aberrant flow in any direction, thus obscuring true flow characteristics.

ULTRASOUND BIOMICROSCOPY
The current generation of commercial ultrasound machines is equipped with 3 to 10 MHz probes, and provide a lateral resolution of up to 0.7–1.0 mm. This level of resolution is sufficient for many clinical uses, but the full potential of image analysis can be exploited with an instrument that provides microscopic resolution (i.e., < 0.2 mm). An “ultrasound biomicroscope” emits a sound wave with a frequency of 25 to 55 MHz and produces an image with a resolution of 30–50 μm (Jaiswal et al. 2009). Detection of small follicles has been validated using histological techniques in mice (Jaswal et al. 2009; Mircea et al. 2009) and surgical approaches developed in rabbit (Cervantes et al. 2013). Major limitations of the biomicroscope are depth of penetration (approximately 10 mm at 30 MHz, 5 mm at 50 MHz), field of view (imaging width, 1 cm), and frame rate (≤ 8 frames per second). Results of studies in cattle document the utility of ultrasound biomicroscopy using a transvaginal approach (Figure 6). Bovine and human follicles as small as 0.4 mm could be detected with high accuracy, the granulosa layer of follicles could be distinguished and the cumulus-oocyte complex was clearly depicted (Baerwald et al. 2009, Pfeifer et al. 2012). A three- to four-fold increase in the number of small follicles (< 3 mm) was detected using the transvaginal approach with ultrasound biomicroscopy compared to conventional ultrasonography and cumulus oocyte complexes were detected in 19% of examined bovine follicles in vivo (Pfeifer et al. 2012). Echotexture analyses of images obtained with the ultrasound biomicroscope have, for the first time, provided dynamic images of the ovary at histologic resolution.

Figure 6. High resolution image of bovine ovarian follicles obtained from an excised ovary (A, C) and by in vivo transvaginal imaging (B, D) with an ultrasound biomicroscope using a 55 MHz (A) or a 25 MHz (B) transducer
The cumulus-oocyte-complex (arrowhead) is clearly visible attached to the wall of a 1.7 mm follicle wall (A) at 11 o’clock and to the wall of a 4.38 mm follicle at 6:30 o’clock (B). C and D illustrate computer-generated surface plots by region analyses of follicles from A and C, respectively. Region analysis allows the examination of never-before seen details of the follicle wall, antrum and the cumulus-oocyte-
complex. Figure D inset shows the area (enclosed within the white line) of ovary that is represented in the main image. The height of the image in C is encoded in color while that of D is encoded in gray-scale; both represent pixel values (Black = 0, white = 255) from the original image. The interface between follicle wall and stroma may be seen on close inspection of D (marked by the double-headed arrow).

**CONCLUSION**

Transrectal ultrasonography has become an indispensable tool for critical assessment of the ovaries and tubular genitalia in the cow. Current applications of ultrasonography in cattle include 1) detection of cyclic versus non-cyclic state, 2) diagnosis of ovarian and uterine pathology, 3) pregnancy and twin diagnosis, 4) fetal viability and fetal loss, and 5) fetal sex diagnosis. Transvaginal ultrasound-guided needle puncture is also becoming a widely used technique to access follicular contents (oocytes, fluid, granulosa cells) and products of the conceptus (amniocentesis, allantocentesis) in a noninvasive way. Ultrasonography in the bull has received more attention recently and is aimed at detection of abnormalities in the internal or external genitalia. New applications involve computer-assisted ultrasound image analysis, 3-dimensional imaging, Doppler ultrasonography of vascular flow, and ultrasound biomicroscopy. New and well-established ultrasound techniques have been extensively
incorporated into research protocols and, as instrumentation becomes more available and affordable, one may anticipate rapid acceptance of these techniques in bovine practice as well.

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One Health and Translational Research: Bovine Model for Understanding Reproductive Function in Women and Monovular Species

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ABSTRACT

Large animal models, particularly bovine, equine and ovine, have been validated for the purposes of understanding ovarian function in women. These models have permitted hypothesis testing to address related issues in women and to formulate new fertility and contraception protocols that are consistent with endogenous ovarian and endocrine rhythmicity. More consistent use of terminology related to the estrous/menstrual cycle and ovarian follicular dynamics will facilitate knowledge transfer, not only among comparative biologists, but also for those involved in the development of new diagnostic and treatment products and protocols. Patterned after studies done in cows, studies of follicular dynamics in women support the wave theory of antral follicle development during the menstrual cycle. The menstrual cycle in women is characterized by 1 or 2 anovulatory follicular waves during the luteal phase, in which a dominant follicle may or may not be manifest, and the ovulatory wave in which the dominant (ovulatory) follicle is selected during the follicular phase. The mechanisms controlling the wave pattern in women have yet to be confirmed, but studies in cattle provide foundational background for examining the role of FSH in wave recruitment, the mechanism of selection of the dominant follicle, the role of the CL in controlling follicular dynamics, the ramifications if a 2- vs 3-wave pattern, and the effects of follicular and maternal aging. Furthermore, results of studies in cows provide an ability to interpret the clinical significance of antral follicle counts, and to anticipate the effects of ovarian stimulation for ovulation induction or suppression for contraception.

INTRODUCTION

The One Health Initiative began in 2006 as a part of the agenda of then-AVMA president Roger K. Mahr (www.onehealthinitiative.com). A year later, the American Medical Association (AMA) partnered with the AVMA on the One Health concept and became an active stakeholder in laying the foundation for and developing the principles of the One Health approach. The One Health Commission was formed in 2009 to promote collaboration across human, animal, and environmental health sciences. The formation of the Commission came at a time of heightened concern by policy makers and public health officials about the potential spread of newly emerging infectious diseases, such as H1N1 influenza, as well increasing threats posed by other emerging zoonotic diseases, food- and water-borne diseases, and environmental change. The emphasis on the One Health concept has been on infectious disease, but we envisage a broader concept that includes normal form and function (i.e., in addition to common diseases, humans and animals have common body morphology and functions - including reproductive physiology).

A research model is a tool to investigate a general phenomenon. Models for biomedical research usually imply the use of specific techniques (e.g., ultrasonography) and experimental units (e.g., animals) with which data are gathered, hypotheses are tested, and patterns are defined to extend a concept into new areas (e.g., different species). Good animal models for biomedical research are those that are
readily accessible (i.e., abundant and inexpensive), malleable (i.e., easy to work with and adaptable), of broad applicability, representative, repeatable, relevant and lend themselves to quantitative assessment. The focus of this review is on how the use of bovine model of follicular dynamics has set the stage for discoveries in women, and how the study of fertility, contraception and reproductive aging has been influenced by these discoveries. A comparative approach is used to emphasize similarities among species in an attempt to develop a unified theory of ovarian follicular development and ovulation among monovular species. Discussion is confined to antral follicle dynamics, with particular emphasis on findings in our laboratory.

Ethical and logistical limitations with human subjects prohibit repeated or prolonged examinations, invasive procedures, or intentional omission of treatment. While laboratory rodents are particularly useful for some aspects of biomedical research, they offer relatively few advantages for the study of ovarian dynamics in humans and larger mammals. Rodents are polytocous species with an extremely short ovarian cycle that includes a luteal phase only if the female is mated. The bovine model for ovarian studies in humans was proposed about 2 decades ago (Adams and Pierson 1995; Singh et al. 2004). Since then, use of the bovine model has resulted in a vast expansion of knowledge regarding ovarian follicular and luteal development in both animals and humans. Similar to women, cows are monovular and polycyclic, and have similar pathologic conditions such as follicular cysts, luteinized anovulatory follicles, and lactation- or stress-related suppression of follicle growth and ovulation (Adams and Pierson 1995). The bovine model offers several advantages. Follicular wave dynamics, ovulation, follicular wave emergence, and temporal relationships among follicles are better characterized in the cow than in any other species, and individual follicles can be monitored over time.

**ESTROUS VS. MENSTRUAL CYCLE**

The pattern of ovarian cyclicity is very similar between domestic animals and primate species, but differing points of reference often lead to confusion and misinterpretation. The “starting point” for the ovarian cycle is based on the most overt event in the respective species (i.e., menstruation in women and estrus in animals). Unfortunately, these two points of reference represent distinctly different physiologic periods of the ovarian cycle.

The menstrual cycle in women is comprised of a follicular phase followed by ovulation in “mid-cycle” and a subsequent luteal phase. The follicular phase (preovulatory follicle development and rising estradiol) and the luteal phase (period of CL growth and regression) each last about 14 days in a typical 28-day menstrual cycle. Menses occupies, on average, the first 5 days of the follicular phase. Low circulating levels of progesterone in the late luteal phase no longer support the thickened endometrium; hence, the endometrial lining is shed during menstruation and the next menstrual cycle begins. During pregnancy, circulating hCG, detectable 9–10 days after ovulation (Del Canto et al. 2007) prevents luteolysis. In contrast to women, the endometrial lining in cow does not undergo periodic shedding and thus there is no menstruation. The reproductive cycle is instead described with reference to sexual receptivity or “estrus.” The cycle may be divided into 4 phases: 1) proestrus, when an ovulatory follicle develops; 2) estrus, the period of “sexual receptivity” when final follicular maturation and ovulation occur; 3) metestrus, the period of CL formation; and 4) diestrus, when the CL is mature and actively produces progesterone (Peter et al. 2009). Proestrus and estrus comprise the follicular phase and
metestrus and diestrus comprise the luteal phase. The duration of the estrous cycle in the cow is approximately 21 days. Unlike primates, the follicular phase of the estrous cycle in cows is shorter than the luteal phase (3–4 days and 16–18 days, respectively). Despite differences in luteal phase length, the growing phase of the dominant ovulatory follicle is comparable in humans and the cow (14 days vs. 11 days, respectively). Rather than referring to menstrual or estrous cycle, from a comparative standpoint, it may be useful to refer to an “interovulatory interval” (IOI; ovulation, luteal phase, follicular phase, ovulation). The IOI has been used for evaluating ovarian follicular dynamics in domestic animals and more recently in women in an attempt to reduce ambiguities in detection methods and definitions used to characterize follicle waves (Baerwald et al. 2003a, b).

Figure 1. Theories of ovarian follicular dynamics during the estrous/menstrual cycle, illustrated from one ovulation to the next (i.e., one interovulatory interval)

Caption: Menses is indicated by the shaded bar along the x-axis and estrus is indicated by the solid bar. The theory of continuous recruitment (A) is that antral follicles grow and regress continuously throughout the interovulatory interval and the ovulatory follicle is the one that happens, by chance, to be at the appropriate stage of development to respond to the preovulatory surge of LH. The theory of a single recruitment episode (B), as described for humans and non-human primates, is that an ovulatory follicle is selected from a single follicular cohort that emerges following luteal regression. The wave theory of follicle recruitment (C), as described for large animals, is that 2 or more cohorts (i.e., waves) of antral follicles are recruited (i.e., emerge) during the ovarian cycle, regardless of phase (luteal or follicular). The dominant follicle that develops in the final wave of the interovulatory interval ovulates while preceding waves are anovulatory. Data from studies in horses and women are consistent with the wave theory of follicle development, but anovulatory follicular waves may have a clear dominant follicle (Major wave; dotted line) or not (Minor wave; D). [Modified from 32].
**Wave Pattern of Antral Follicle Development**

Three schools of thought have evolved to explain antral follicular development (Figure 1) during the menstrual/estrous cycle:

1. **Continuous recruitment theory**: Antral follicular growth and regression occurs continuously, independent of the phase of the reproductive cycle;
2. **Single recruitment episode theory**: During a “privileged phase” of the ovarian cycle, one or several follicles emerge from an underlying reservoir of small antral follicles and reach maturity during the ensuing estrus or follicular phase; and
3. **Follicular wave theory**: Antral follicles develop in a wave-like fashion during the ovarian cycle, irrespective of phase (Rajakoski 1960).

The introduction of real-time ultrasonography permitted rigorous test of the wave theory of follicular dynamics in cattle (Knopf *et al.* 1989; Pierson and Ginther 1987), and led to critical characterization of the wave pattern (discussed below). Using studies in cattle as an example, serial ultrasonographic monitoring of individually identified follicles with endocrine profiling has since been used to document the wave pattern of follicular development in every species in which it has been examined, including sheep (Ginther *et al.* 1995; Ravindra *et al.* 1994), goats (Ginther and Kot 1994), horses (Bergfelt and Ginther 1993; Ginther and Bergfelt 1993), camels (Adams *et al.* 1990), wild ungulates (Hoare *et al.* 1997; McCorkell *et al.* 2007; Palomino *et al.* 2013), and women (Baerwald *et al.* 2003a, b). A “wave” has been defined as the synchronous growth of a group of antral follicles at regular intervals during the ovarian cycle (Figure 1).

Over 95% of estrous cycles in cattle are comprised of 2 or 3 follicular waves (Figure 2), and the pattern has a propensity for repeatability within individuals [reviewed in Adams 1999]. Wave emergence is defined as the synchronous growth of about 20 follicles (follicular wave), initially detected by ultrasonography at 3–4 mm diameter. One of these follicles is “selected” for preferential growth (dominant follicle) by Day 3 of the wave, while the remainder (subordinates) undergoes atresia. Emergence of successive waves is preceded by a surge in systemic FSH concentrations followed by a nadir (Adams *et al.* 1992b). The development of all follicles, except the ovulatory follicle, may be divided into growing (increasing diameter), static (no change in diameter) and regressing (decreasing diameter) phases (Ginther *et al.* 1989a,b; Ginther *et al.* 1989c,d). In both 2- and 3-wave estrous cycles, emergence of the first follicular wave occurs consistently on the day of ovulation (Day 0). Emergence of the second wave occurs on Day 9 or 10 for 2-wave cycles, and on Day 8 or 9 for 3-wave cycles (i.e., 1 or 2 days earlier). In 3-wave cycles, a third wave emerges on Day 15 or 16. The dominant follicle present at the onset of luteolysis becomes the ovulatory follicle. The corpus luteum begins to regress earlier in 2-wave cycles (Day 16) than in 3-wave cycles (Day 19) resulting in a correspondingly shorter estrous cycle (20 days vs. 23 days, respectively). Hence, the often-cited 21-day cycle of cattle exists only as an average of 2- and 3-wave interovulatory intervals.
Figure 2. Dynamics of ovarian follicular development and gonadotropin secretion during 2-wave and 3-wave estrous cycles in cattle

Caption: Dominant and subordinate follicles are indicated as open (viable) or shaded (atretic) circles. A surge in circulating concentrations of FSH (black line) precedes emergence of each wave. A surge in circulating concentrations of LH (blue line) precedes ovulation. The LH surge is preceded and succeeded by a period of high LH pulse frequency as a result of low circulating concentrations of progesterone (i.e., period of luteolysis and luteogenesis, respectively) [modified from Adams et al. 2008].

The most prevalent textbook description of human follicular development is that antral follicles are recruited continuously during the menstrual cycle and that the follicle destined to ovulate emerges during the follicular phase. However, based on earlier studies in cattle, more recent research involving daily transvaginal ultrasonography and concurrent endocrine profiling has documented a wave-pattern of antral follicle development during the menstrual cycle in women [Figure 3; Baerwald et al. 2003a,b]. A cohort of 4–14 follicles ≥ 5 mm was recruited either 2 or 3 times during the menstrual cycle. In women with 2 follicular waves, an anovulatory wave emerged at the time of ovulation (i.e., start of the luteal phase) followed by emergence of the ovulatory wave during the early follicular phase. In women with 3 waves, an anovulatory wave emerged at the time of ovulation, a second anovulatory wave emerged during the mid- to late-luteal phase, and a third wave (the ovulatory wave) emerged in the early to mid-follicular phase (Baerwald et al. 2003b). Menses occupies, on average, the first 5 days of the follicular phase; however, the event of menses was unrelated to follicular wave emergence. Women with 3
follicular waves (66% of women) had a significantly longer interovulatory interval (29 days) compared to women with 2 waves (27 days); hence, the often-cited 28-day menstrual cycle exists only as an average of 2- and 3-wave interovulatory intervals.

**ONE HEALTH (ONE PHYSIOLOGY): COWS AS A RESEARCH MODEL**

Interventional studies, particularly in cattle, have been useful for interpreting temporal relationships observed in studies of the menstrual cycle in women. The following are some examples of questions relevant to our understanding of ovarian function in women that have been addressed through the use of large animal models.

**Association Between Plasma FSH and Wave Dynamics**

A series of studies using the bovine model clearly documented that each follicular wave is preceded by a surge in circulating FSH and that cows with 2-wave cycles have 2 FSH surges and 3-wave cycles have 3 surges (Figure 2) (Adams et al. 1994; Adams et al. 1993a; Adams et al. 1993b; Adams et al. 1992b; Berfert et al. 1994; Bodensteiner et al. 1996; Gibbons et al. 1997; Gong et al. 1995; Sunderland et al. 1994). Emergence of a follicular wave occurs during the FSH surge [reviewed in Adams et al. 2008] and the following nadir in FSH effectively prevents new wave emergence. The decline in circulating FSH is a result of negative feedback from products of the emerging follicles (Adams et al. 1993a; Adams et al. 1993b; Adams et al. 1992b; Gibbons et al. 1997). These findings have had important implications for the design of more effective synchronization and superstimulation protocols in cattle (Bo et al. 1995).

Temporal events during the menstrual cycle in women are consistent with findings in cattle. In humans, the wave-eliciting surge in circulating FSH spans a period of about 4 days (Adams et al. 2008; Baerwald et al. 2003a), but, unlike cows, the magnitude of the FSH surge preceding the first wave of the interovulatory interval (i.e., associated with the preovulatory LH surge) appears to be greater than that of other waves in women (Baerwald et al. 2003a). Inhibin from the recruited follicles prevents continued FSH secretion in the mid-follicular phase in women (Groome et al. 1996; van Santbrink et al. 1995), consistent with findings in cattle.

**Dominant Follicle Selection in the Bovine Model and Women**

In cattle, a transient rise in FSH permits sufficient follicular growth so that one follicle acquires LH responsiveness with the ability to survive without FSH. The time of dominant follicle selection coincided with the first significant drop in FSH concentrations (Adams et al. 1992b). About 2 days after wave emergence, the follicle destined to become dominant has more LH receptors than subordinate follicles. Subordinate follicles can, however, achieve dominance if the original dominant follicle is removed (Adams et al. 1993b; Gibbons et al. 1997) or if exogenous FSH is supplied (Adams et al. 1993a). Until recently, selection of a dominant follicle was thought to occur only once during the menstrual cycle (Baird 1987; Gougeon and Lefevre 1983). However, recent results document that selection of a dominant follicle is a frequent occurrence in anovulatory waves (Baerwald et al. 2003a,b). Nearly a quarter of anovulatory waves in both 2- and 3-wave patterns in women were characterized as major waves (i.e., there was clear manifestation of follicular dominance) (Baerwald et al. 2003a; Ginther et al. 2005; Ginther et al. 2004). Most women developed a major ovulatory wave in the follicular phase and 1 or 2 minor anovulatory waves in the preceding luteal phase (Figures 1 and 3). Morphologic changes and
growth dynamics of dominant and first subordinate follicles in women are similar to those described in other monovular species (cows and mares) (Ginther et al. 2001; Mihm and Evans 2008). The mechanism of selection and follicular dominance, however, remains unclear, and reasons for the manifestation of major and minor waves are yet unexplained.

Figure 3. Ovarian and endocrine changes during the human menstrual cycle (2-wave pattern only)

Caption: Data are presented to encompass both 1 complete interovulatory interval and 1 complete menstrual cycle. Dotted vertical lines indicate the days of wave emergence. Follicles are shown as spherical structures with a cavity, the CL is shown as an irregular shaded structure after ovulation. The anovulatory wave was characterized by an increase in follicle numbers and clear follicular dominance (major wave, ghosted follicle) or no clear dominance (minor wave) prior to the ovulatory wave (Modified from Baerwald et al. 2012).

The mechanism of selection appears to be one of hierarchical suppression of follicles within a wave, rather than an all-or-none process. In a study designed to characterize the developmental pattern of small (1- to 3-mm) follicles in cattle (Jaiswal et al. 2004), the future dominant follicle emerged 6 to 12 h earlier than the first subordinate follicle and maintained a size advantage from the time of first
detection. The authors concluded that: i) 1 to 3 mm follicles develop in a wave-like manner in association with surges in plasma concentrations of FSH; 2) 1 to 3 mm follicles are exquisitely responsive to transient elevations in FSH (i.e., within 6 h); and 3) selection of the dominant follicle is manifest earlier than previously documented and is characterized by a hierarchical progression over a period encompassing the entire FSH surge (5 days). That is, follicles emerging progressively later in the wave had a progressively smaller diameter profile and regressed progressively sooner in response to the decline in FSH than those that emerged earlier in the wave (Figure 4).

Figure 4. Growth of dominant and subordinate follicles in cattle (n = 9) relative to the peak in plasma FSH concentrations (mean ± SEM)

Caption: FSH concentrations changed over time (p < 0.01). Transient increases in FSH were followed within 6 hours by transient increases in the growth rate of the 3 largest follicles. Successive slowing of the growth rate of the third, second, and first largest follicles of a wave during the decline in the FSH surge suggests that the selection mechanism involves sequential suppression of progressively larger follicles over a period of 72 h (i.e., selection hierarchy).

ab. Values with no common superscript are different (p ≤ 0.05). [Modified from Jaiswal et al. 2004]

Role of Progesterone in Controlling Follicular Dynamics

The CL is the primary source of progesterone and under the influence of progesterone (e.g., diestrus) successive follicular waves are anovulatory. The dominant follicle present at the onset of luteolysis becomes the ovulatory follicle (Kastelic and Ginther 1991). Progesterone or progestogens suppress LH pulse frequency (Fortune 1994; Savio et al. 1988), which in turn suppresses dominant follicle growth (Adams et al. 1992a). Whereas progesterone suppresses LH secretion, results clearly demonstrate that progesterone does not suppress FSH secretion in vivo (Adams et al. 1992a). Suppression of FSH and follicular wave emergence has been attributed primarily to estradiol and inhibin. In cattle, the primary source of estradiol and inhibin is from the dominant and subordinate follicle. Estradiol content in the follicular fluid of the growing dominant follicle increases at least 20-fold by the day of selection (3 d after
wave emergence), followed by a 3-fold decrease by the early static phase of the anovulatory dominant follicle (6 d) before returning to baseline in the early regressing phase (11 d) (Singh et al. 1998). In contrast, products of the CL in women and non-human primates (estradiol and inhibin A) are thought to be responsible for suppressing FSH and thereby preventing the development of follicles > 4 mm during the luteal phase (Chikazawa et al. 1986; Devoto et al. 2009; Gougeon and Lefèvre 1983; Groome et al. 1996; McLachlan et al. 1987; McNatty et al. 1983; Mikhail 1970; Roberts et al. 1993; Savard et al. 1965; Smith et al. 1990). As a result, circulating FSH concentrations rise at the transition from the luteal to follicular phase (Le Nestour et al. 1993; Roseff et al. 1989). This rise in FSH is responsible for preventing atresia of a cohort of small (2–5 mm) antral follicles in each ovary (Hodgen 1982; Koering 1969; McNatty et al. 1983; Pache et al. 1990; van Santbrink et al. 1995). Estrogens, androgens and inhibin B produced by follicles of the recruited cohort (Fraser et al. 1999; Gougeon 1996; Groome et al. 1996; Laven and Fauser 2004) act in an endocrine manner to inhibit continued FSH secretion in the mid-follicular phase (Groome et al. 1996; van Santbrink et al. 1995).

**Reproductive Aging in Women and Cows**

Endocrine and ovarian characteristics of reproductive aging were characterized in a series of studies in which old cows (≥ 15 years) were compared with their young daughters (≤ 5 years) (Malhi et al. 2007, 2008; Malhi et al. 2006; Malhi et al. 2005). Mean circulating FSH concentrations were consistently higher in old cows than in their daughters, but the expected pattern of FSH secretion and wave emergence was maintained in old cows. Despite elevated FSH, fewer 4 to 5 mm follicles were recruited into each follicular wave in old cows than in their daughters. The duration of the interovulatory and interwave intervals did not change with age, but the ovulatory follicle of old cows with a 2-wave pattern was smaller at the time of ovulation than that of young cows. There was no age effect on circulating LH concentrations or LH pulse frequency. In a study of the ovarian response to superstimulatory treatment (Malhi et al. 2008), fewer small (< 5 mm) follicles were recruited into the follicular wave, and fewer follicles in all size categories developed after ovarian superstimulation in old cows than in their young daughters. Lastly, data from a study in which embryos from old cows and their daughters were transferred to age-matched recipient cows (Malhi et al. 2007) revealed that the oocytes from old cows were markedly less competent and produced only half as many embryos as their daughters.

Decreased fertility with maternal aging has been well documented in cattle and humans (Erickson et al. 1976; Klein and Sauer 2001; Stensen et al. 2010). Infertility in older women has been associated with a dwindling primordial follicular pool, a lower antral follicle count, altered hormone secretions, decreased conception rate, meiotic abnormalities and increased gestational attrition (Burger et al. 2002; Gosden and Faddy 1994; Klein and Sauer 2001; Klein et al. 1996; Kuliev et al. 2005; Santoro et al. 2003; Soules et al. 2001). Consistent with the above-mentioned studies in cattle, circulating concentrations of FSH in women increased in late reproductive stages (Gosden and Faddy 1994; Santoro et al. 2003; Soules, et al. 2001); the increase has been attributed to reduced inhibin B secretion (Broekmans et al. 2009; Burger et al. 2002; Klein et al. 1996; Klein et al. 2004; Santoro et al. 2003; Soules et al. 2001). Circulating concentrations of anti-Mullerian hormone gradually declines in women with age, in association with a decrease in antral follicle count [reviewed in Broekmans et al. 2004]. Reproductive aging in women has also been associated with a shortened follicular phase and thus, a shortened
menstrual cycle (Klein et al. 1996). Pregnancy rates decline exponentially in women over 35 years of age; i.e., 39% chance of a live birth per cycle at < 35 years of age, 20% at 38–40 years, and < 6% at > 43 years (CDCP et al. 2010). Interestingly, fertilization and cleavage rates do not change with age (Schwartz and Mayaux 1982), but frequent arrests at the morula stage, reduced blastocyst expansion (Janny and Menezo 1996), and an increased incidence of aneuploidies (Pellestor et al. 2003) have been associated with maternal age (CDCP et al. 2010; Cohen et al. 1999). Abnormal numbers, shapes, aggregation patterns and mutations in mitochondrial genes have been reported in human and bovine zygotes and early embryos that fail to develop (Chao et al. 2005; Eichenlaub-Ritter et al. 2004; Liu et al. 2002; Thouas et al. 2005). However, it is far from clear which of these factors plays the major role during maternal and follicular aging.

Basic Studies to Clinical Applications

Antral Follicle Count
In cattle, the number of follicles detectable by ultrasonography varies widely among individuals and according to follicular wave status (Burns et al. 2005; Jaiswal et al. 2004; Jaiswal et al. 2009; Singh et al. 2004); however, the intrinsic number of follicles at wave emergence is highly repeatable within individuals (Burns et al. 2005; Singh et al. 2004). In a direct comparison of high-follicle count vs. low-follicle count cows (Singh et al. 2004), the number of follicles recruited into a wave was highly correlated with the number of follicles recruited into successive waves, and the superstimulatory response was highly correlated with the number of follicles recruited into a follicular wave for a given individual. This characteristic now forms the basis of a simple ultrasound test to predict the superstimulatory response in cattle. Similar to cattle, antral follicle count in women (i.e., number of 2–10 mm follicles) has been used as a marker of reproductive potential and as a predictor of ovarian response to superstimulation (Almog et al. 2011; Broekmans et al. 2004; Hsu et al. 2011; Styer and Toth 2011). Declining antral follicle count has been linked to the loss of fertility at the onset of menopause (Broekmans et al. 2004). For clinical purposes, antral follicle counts are usually assessed approximately 3 days after the onset of menses (i.e., ostensibly at the beginning of the emergence of the ovulatory wave). However, detailed study of follicular waves document that antral follicle counts change significantly during the menstrual cycle in women (Baerwald, et al. 2003a). Based on the observation that the onset of menses is unrelated to follicular wave emergence (Baerwald et al. 2003a), there is rationale for revising the clinical practice of a day 3 antral follicle count.

Ovarian Stimulation
The patterns of follicular wave development and follicular dominance have important implications on ovarian response to gonadotropin stimulation. Results of studies in cattle have documented that the superstimulatory response is 1) inferior when treatment is initiated after selection of the dominant follicle; 2) greater when treatment is initiated within ± 1 day of wave emergence; and 3) similar between Wave 1 (rising progesterone) and Wave 2 (high-endogenous progesterone) [reviewed in Singh et al. 2004]. As a result of these findings, superstimulatory protocols in cattle now incorporate synchronization of follicular wave emergence. Thousands of women per year undergo ovarian superstimulation for assisted reproduction in Canada. Approximately 10–25% of women develop an
abnormally low number of dominant follicles during ovarian stimulation; as a result, the potential for conception and subsequent pregnancy is reduced and the stimulation cycle may be cancelled (Kyrou et al. 2009). There is an obvious need for optimizing treatment outcomes in women undergoing ovarian stimulation. Recent studies in women, based on those previously conducted in cattle, showed that synchronizing the initiation of ovarian stimulation with the expected time of follicle wave emergence increases the number of mature follicles [reviewed in Baerwald et al. 2012]. In this regard, the bovine model may be used experimentally to test ovarian responses to new treatment protocols and pharmaceuticals, without risk to women (e.g., effects of aromatase inhibitors) (Yapura et al. 2011).

**Hormonal Contraception**

Studies to characterize ovarian follicular wave dynamics in women, based on those previously conducted in domestic farm animals, have had implications for understanding the mechanisms underlying different types of hormonal contraceptives and for developing safe and efficacious contraceptive formulations. The type and dose of estrogen and progestin comprising the contraceptive formulation determines the degree of suppression of antral follicle development. Ultrasonographic monitoring of women on hormonal contraceptives revealed that 85% of antral follicle development originates during the hormone-free interval (Baerwald et al. 2004). Withdrawal of exogenous progesterone and estradiol resulted in emergence of a new wave of antral follicles, some of which included selection of a dominant (i.e., estrogenic) follicle capable of ovulating. The number of dominant follicles detected appears to be inversely related to the dose of ethinyl estradiol (Baerwald et al. 2004); the role of different progestins in influencing antral follicle development during the hormone-free interval is less well understood. From a clinical perspective, missed pills that extend the hormone-free interval place women at a greater risk of dominant follicle development. Newer contraceptive formulations reduce the duration of the hormone-free interval or remove it altogether. In addition, initiation of hormonal contraceptive treatment in the presence of a dominant follicle may not provide enough suppression to prevent ovulation; the larger the dominant follicle at the time of initiation, the greater the chance of ovulation (Baerwald et al. 2006).

**SUMMARY**

Critical studies of the characteristics and control of ovarian follicular and luteal dynamics in cattle have involved frequent (i.e., daily or multiple times a day) blood sampling and ultrasonography. Studies of this nature in women are difficult or prohibitive. Differences in antral folliculogenesis between humans and animals appear to be more in detail rather than in essence, and may reflect differences in intrinsic physiology or merely differences in our ability to detect changes in a given species. In women, the presence of endometrial shedding and symmetric luteal and follicular phases are different from that observed during the estrous cycles of domestic farm animals but despite these differences, general similarities in antral follicular dynamics exist. A continuous pattern of antral follicle development was originally proposed in domestic livestock species; however, the use of frequent serial ultrasonography and simultaneous endocrine profiling in these animal species has resulted in a broad understanding of follicular wave dynamics. Follicular waves have now been described in every species in which this approach has been used, including humans. The relatively large diameters of antral follicles in cows and
mares, compared to monkeys, sheep, and rodents provide greater feasibility for characterizing antral follicular dynamics ultrasonographically. While the use of large animal models has increased our understanding of ovarian function and provides the hypothetical basis for studies in women, differences in vocabulary, culture, and research methodologies has hampered knowledge translation. These differences represent a systemic impediment to a broad understanding of ovarian function and limits progress and innovation in the development of safer and more efficacious treatments for infertility and contraception.

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Theory and Practice of Ovarian Synchronization and Superstimulation in Cattle
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INTRODUCTION
In theory, effective and reliable control of the estrous cycle and ovulation in cattle permits efficient and prescheduled use of farm resources for the purposes of herd breeding management. Important underlying assumptions, however, are that the methods used to control ovarian function are consistent with, and management practices (e.g., nutrition) are conducive to, normal endogenous rhythms. The following is intended to provide an understanding of the theory behind the myriad techniques that have evolved to induce ovarian synchronization and superstimulation in cattle, and how new approaches are designed to take advantage of normal ovarian function in cattle for optimal response. This is not intended to be a comprehensive review, but rather to highlight the evolution of approaches to synchronization and superstimulation in relation to our understanding of ovarian physiology. For brevity, reference is made to reviews of specific topics rather than original studies. Unless otherwise stated, the information presented is from results of studies on Bos taurus.

FOLLICULAR AND LUTEAL DYNAMICS DURING THE NORMAL ESTROUS CYCLE
Follicular growth in cattle occurs in a wave-like fashion, and the majority (i.e., > 95 %) of estrous cycles in cattle are comprised of two or three such waves (reviewed in Adams et al. 2008; Jaiswal et al. 2009). Follicular wave emergence in cattle is characterized by the sudden (within 2 to 3 d) growth of 8 to 41 small follicles that are initially detected by ultrasonography at a diameter of 3 to 4 mm (Figure 1; reviewed in Adams 1999). The growth rate is similar among follicles of the wave for about 2 d, after which one follicle is selected to continue growth (dominant follicle) while the rest become atretic and regress (subordinate follicles). The dominant follicle suppresses the growth of the subordinates in the existing wave, and suppresses the emergence of the next follicular wave (Adams et al. 1992a, 1993). Under the influence of progesterone (e.g., diestrus), dominant follicles of successive waves undergo atresia. The dominant follicle present at the onset of luteolysis becomes the ovulatory follicle, and emergence of the next wave is delayed until the day of the ensuing ovulation. The CL begins to regress earlier in 2-wave cycles (Day 16) than in 3-wave cycles (Day 19) resulting in a correspondingly shorter estrous cycle (19 to 20 d versus 22 to 23 d, respectively). Hence, the so-called 21-d estrous cycle of cattle exists only as an average between 2- and 3-wave cycles (Figure 1).

Two Ovaries - One Unit
The two ovaries act as a single unit (i.e., each follicular wave includes follicles from both ovaries that respond in unison). In a critical study of intraovarian relationships (Ginther et al. 1989), the authors concluded that the dominant follicle suppresses subordinates and new wave emergence via systemic (endocrine) rather than local channels. Only one follicle from the pair of ovaries is selected to become dominant, the side of dominant follicle development was random, and the dominant follicle was equally likely to reside in the same or contralateral ovary to that of the largest subordinate follicle. The side of the CL or dominant follicle of a previous wave had no effect on the side of the ovulatory follicle.
Although intrafollicular (autocrine and paracrine) factors are important for growth, health and demise of an individual follicle, there is no convincing in vivo documentation of one follicle affecting the health/regression status of its neighbors directly by a localized effect.

**Figure 1. Dynamics of ovarian follicular development and gonadotropin secretion during 2-wave and 3-wave estrous cycles in cattle**

Caption: Dominant and subordinate follicles are indicated as open (viable) or shaded (atretic) circles. A surge in circulating concentrations of FSH (red line) precedes emergence of each wave. A surge in circulating concentrations of LH (yellow line) precedes ovulation. The LH surge is preceded and succeeded by a period of high LH pulse frequency as a result of low circulating concentrations of progesterone (i.e., period of luteolysis and luteogenesis, respectively) (Modified from Adams et al. 2008).

**2-wave interovulatory interval**

![2-wave interovulatory interval diagram](image)

**3-wave interovulatory interval**

![3-wave interovulatory interval diagram](image)

**Gonadotropins and Follicular Waves**

Emergence of a follicular wave and selection of the dominant follicle are temporally associated with a rise and fall in circulating concentrations of FSH (Figure 1; Adams et al. 1992a). Emergence of a follicular wave is preceded by a surge in plasma FSH concentrations in both spontaneous waves and induced waves. Follicular products (estradiol and inhibin), especially those from the dominant follicle are responsible for suppressing FSH release and, therefore, the emergence of the next follicular wave.
(Figure 1). At the end of the period of dominance (i.e., at ovulation, or the mid-static phase of an anovulatory dominant follicle), circulating concentrations of FSH begin to rise. Levels rise 1.5- to 2-fold over the next 2 d and peak about 12 to 24 h before emergence of the new wave, when the future dominant follicle is 4 to 5 mm in diameter. If an existing dominant follicle is removed (e.g., follicular ablation), a surge in FSH begins within the next 12 h and results in emergence of a new follicular wave within 24 h (Bergfelt et al. 1994). Selection of the dominant follicle is associated with decreasing levels of FSH in circulation during first 3 d of the wave. The nadir in FSH is reached 4 d after wave emergence and levels remain low for next 2 to 3 d. Receptors for FSH are present only on granulosa cells, while LH receptors are located on both granulosa and theca cells in the wall of antral follicles. The dominant follicle acquires more LH receptors on its granulosa cells than its subordinates and is therefore able to shift its gonadotropin dependence to LH during the FSH nadir, and continue to grow while the subordinates regress.

**Hormonal Interplay**

The CL is the main source of progesterone, and CL morphology and plasma progesterone concentration are good indicators of progesterone synthesis within the CL (reviewed in Singh et al. 2003). Intense angiogenesis, proliferation of granulosa and theca cells from the wall of ovulated follicle, and their differentiation (luteinization) during the first 5 to 6 d after ovulation (metestrus) results in a progressive increase in plasma progesterone concentration from < 1 ng/mL at 3 d after ovulation to about 3 ng/mL by 6 d. Plasma progesterone concentration peaks between 10 and 14 d postovulation (greater than 4 ng/mL) followed by decreasing levels after 16 d due to luteolysis (hypoxic cell death resulting from hyalinization of blood vessels) induced by PGF2α released from the endometrium of the nonpregnant cow.

Dominant follicles from both anovulatory and ovulatory waves produce estradiol. Theca cells are required for conversion of pregnenolone/progesterone to androgens, while the aromatase enzyme for androgen to estradiol conversion is exclusively localized in granulosa cells. After wave emergence, estradiol content in the follicular fluid of the growing dominant follicle increases at least 20-fold by the day of selection (3 d after wave emergence), followed by a 3-fold decrease by the early static phase of the anovulatory dominant follicle (6 d) before returning to baseline in the early regressing phase (11 d; Singh et al. 1998). Peak estradiol concentration in the follicular fluid of the ovulatory follicle is twice as high as the peak in anovulatory dominant follicles. In addition to estradiol, which has a major inhibitory action on FSH, growing follicles produce other factors such as IGFs, inhibins and follistatin (reviewed in Baerwald et al. 2012; Singh et al. 1999) that also regulate FSH release and availability. Although the dominant follicle plays a major role, all follicles of an emerging wave contribute to suppression of the wave-eliciting FSH surge (Ginther et al. 2000).

The release of both FSH and LH is induced by pulses of GnRH from the hypothalamus, but because FSH release is profoundly influenced by follicular products and because its half-life in cattle is longer than that of LH, episodic release of FSH is less apparent than LH. Pulse frequency and amplitude of LH are influenced by circulating concentrations of both progesterone and estradiol. High levels of progesterone produced by a functional CL during diestrus or pregnancy suppress LH pulse frequency (Figure 1). Plasma progesterone concentrations of about 1.7 ng/mL resulted in 6 LH pulses per 8 h with
an amplitude of 0.2 ng/mL, while progesterone concentrations of 5 ng/mL resulted in only 1.8 pulses per 8 h with an average amplitude of 0.34 ng/mL (Rahe et al. 1980; Kojima et al. 2003). Therefore, dominant follicles grow larger and remain dominant for a longer period of time when LH pulse frequency is elevated (i.e., low progesterone; Adams et al. 1992b; Stock & Fortune 1993). Increasing estradiol levels with decreasing progesterone after luteolysis increase LH pulse frequency further, culminating in a large preovulatory surge.

Synchronization of Estrus & Ovulation

Elective abbreviation or prolongation of the luteal phase can result in induction of estrus and ovulation within a predictive range of 4 days; a sufficiently wide range that obviates prescheduled insemination (fixed-timed insemination or breeding by appointment). The variation in interval to estrus and ovulation in response to luteal phase intervention has been attributed to variations in follicular wave status at the time of treatment. Follicular waves may be controlled by a number of hormonal and physical treatments, and protocols designed to control both luteal and follicular status have resulted in synchronization precise enough to permit fixed-time insemination, and eliminate the need for estrus detection.

Prostaglandin

Enucleation of the corpus luteum is one of the oldest approaches used for estrus manipulation or treatment for ovarian irregularities. In the early 1970s, prostaglandin F2α (PGF) was found to be the natural luteolysin (reviewed in Adams 1998), and since that time PGF has become the most commonly used treatment for elective induction and synchronization of estrus in cattle. Early studies showed that the maturity of the CL at the time of PGF treatment influenced the luteolytic response (reviewed in Adams 1998); PGF did not effectively induce luteolysis during the first 5 or 6 days following estrus. Lack of responsiveness was thought to be a result of a lack of PGF receptors in immature CL, but later work refuted this theory by demonstrating the presence of PGF receptors in CL as early as 2 days after ovulation (Wiltbank et al. 1995). However, it appears that mature CL may possess a positive feedback loop that results in intraluteal PGF production, which may continue the process of luteolysis initiated by a single treatment of exogenous PGF (Wiltbank 1997). If this notion is correct, and immature CL do not possess the positive feedback loop, then multiple injections of PGF may be expected to complete the luteolytic process in early stage CL. In this regard, luteolysis and ovulation was induced in 56/60 heifers (93%) given PGF in the morning and evening of the 4th or 5th day after estrus in two studies (Adams et al. 1994; Nasser et al. 1993).

Transrectal palpation and treatment of cattle with an apparently responsive CL should increase the proportion that respond to PGF treatment, but errors in CL assessment and failures in estrus detection result in only about 75% of treated cattle being detected in estrus (Gaines et al. 1993). Furthermore, in cows in which luteolysis is effectively induced by PGF treatment, the ensuing estrus is distributed over a 6-day period (Figure 2; Seguin 1987). The most consistent response (i.e., the least variability in interval to estrus) resulted from PGF treatment during early diestrus (7 and 8 days after estrus) and later diestrus (15 days after estrus) than from treatment during mid-diestrus (10 to 13 days after estrus; Seguin 1987; Tanabe & Hann 1984). Later studies documented that much of this variation is due to
follicular wave status at the time of treatment. Treatment when the dominant follicle of a wave is in the late growing (≥ 9 mm) or early static phase will result in ovulation of that follicle within 2 to 3 days, whereas treatment after the mid- to late-static phase (i.e., when it is no longer viable) will result in ovulation of the dominant follicle of the next wave 4 to 5 days after treatment. That is, if PGF is given at the end of the period of functional dominance of one follicle, several days are required for a new dominant follicle to grow sufficiently to ovulate (Kastelic et al. 1990, 1991; Savio et al. 1990). With reference to follicular waves (Figure 1), loss of dominant follicle viability is reflected in a new surge in FSH; therefore, the longest intervals from PGF treatment to ovulation may be expected when treatment is given at the time of new wave emergence (i.e., at the time of the FSH surge) 10 to 13 days after estrus (for 2- and 3-wave cycles), and again at 15 to 17 days after estrus (for 3-wave cycles). In a conventional 2-dose PGF synchronization scheme, an interval of 10 or 11 days between doses has been used because it represents the mid-point of the estrous cycle and theoretically all cows should have a PGF-responsive CL at one or both treatments. Based on follicular dynamics, however, a shorter (8 to 9 days) or longer (13 to 14 days) interval between treatments may result in greater synchrony. In this regard, one study reported a higher conception rate using a 14-day rather than an 11-day interval between PGF treatments (Folman et al. 1990).

Figure 2. Distribution of estrus (left) in cattle subsequent to PGF treatment alone (n = 280; Seguin, 1987), and ovulation (right) subsequent to transvaginal ultrasound-guided follicle ablation followed by PGF 4 days later (n = 32; Bergfelt et al. 1994), or follicle ablation plus PGF 4 days later plus LH or GnRH 1 day after PGF (n = 23; Brogliatti et al. 1998).

Numerous innovative treatment regimens based on the use of PGF have been reported for natural breeding or artificial insemination programs, with or without heat detection. A 5-day estrus monitoring and insemination period before and after PGF treatment can be very effective, but estrus detection and breeding are spread over 10 days. If < 20% of the cattle are detected in estrus by the 5th day, then the cattle are either noncyclic, or estrus detection is poor. One approach to minimize investment of time and labor involves PGF treatment of all cows 96 hours after the start of bull exposure. The notion is that cattle bred before PGF treatment will have an immature CL that will not be affected by PGF (Whittier et al. 1991). Another protocol developed for use in dairy herds involves PGF treatment at 14-day intervals (Fuhrman 1993; Furguson & Galligan 1993). Estrus is induced as close as possible to the desired time of first insemination by giving PGF 3 to 17 days before the end of the voluntary postpartum waiting period.
These cows are treated again 14 days later and inseminated according to signs of estrus. Cows not detected in estrus are treated again 14 days later and inseminated upon signs of estrus or at 80 hours after treatment if estrus is not detected. More recently, PGF treatment has been combined with follicle ablation, estrogen/progestogen treatment, or GnRH treatment to better control follicular status and induce more precise synchrony of ovulation (discussed below).

**Follicle Ablation**

Results of 2 experiments in which the dominant follicle was ablated by electrocautery during laparotomy, demonstrated that removal of the dominant follicle hastened the emergence of the next wave (reviewed in Adams 1999). Based on these results, studies have been done to test the hypothesis that transvaginal ultrasound-guided follicle aspiration, as a method of follicle ablation, will induce synchronous wave emergence and ovulation in heifers selected at unknown stages of the estrous cycle (Bergfelt et al. 1994). A luteolytic dose of prostaglandin was given 4 days after transvaginal ablation of all follicles ≥ 5 mm in diameter. Emergence of a new follicular wave was detected within 2 days of ablation, and although the mean length of the interval from prostaglandin treatment to ovulation was not different between the ablation and control groups (5 days), the variability in the length of the interval was significantly diminished in the former (Figure 2). Ovulation occurred in 13/16 heifers (81%) 3 to 5 days after prostaglandin treatment in the ablation group, whereas only 8/17 control heifers (47%) ovulated during the same period. In addition, significantly more follicles were recruited into the ovulatory wave in the ablation group and 3/16 heifers developed double dominant follicles, 2 of which had double ovulations. Transvaginal ultrasound-guided follicle ablation also induced synchrony of follicle wave emergence among calves at 6 months of age; wave emergence occurred 1.6 days (range, 1 to 2 days) after ablation (Brogliatti et al. 1997). The ablation (Day 0) plus prostaglandin (Day 4) protocol was followed by LH or GnRH treatment (on Day 5) to further enhance ovulation synchrony in mature cattle (Brogliatti et al. 1997). LH and GnRH treatments were equally efficacious in reducing the interval to ovulation and in improving synchrony (i.e., less variance) compared to ablation plus prostaglandin alone. Of 23 heifers treated with either LH or GnRH after ablation, all ovulated within the same 24-hour period, and 19 ovulated within the same 12-hour period (Figure 2). Follicle ablation itself is a relatively more involved procedure than an injectable treatment; however, the technique is easily mastered and can be accomplished in minutes without the need of epidural anesthesia.

**Progestosterone**

Progestosterone or progestogens suppress LH pulse frequency, which in turn causes suppression of dominant follicle growth (reviewed in Adams et al. 1999). Whereas progesterone suppresses LH secretion, results clearly demonstrate that progesterone does not suppress FSH secretion *in vivo* (Adams et al. 1992b). Hence, progesterone treatment will slow the growth of LH-responsive follicles (i.e., primarily the dominant follicle) and will prevent ovulation, but it will not stop or synchronize regular periodic FSH surges and emergence of follicular waves.

Although early studies documented the synchronizing effects of progestogen treatment, the synchronized estrus was associated with lowered fertility and recent studies have implicated the development of oversized follicles as a cause. The corollary to progesterone-induced follicle suppression is the relative lack of suppression in the presence of low progesterone. Growth of the dominant follicle
is suppressed in a dose-dependent fashion (Adams et al. 1992b); exposure to above-normal, normal, and below-normal luteal phase progesterone levels, respectively, resulted in undersized, normal, and oversized dominant follicle profiles. Doses of progestogens commonly used to control the estrous cycle in cattle (norgestomet implants, melengestrol acetate in feed, progesterone-releasing intravaginal devices) have relatively less suppressive effects on LH secretion compared to the normal luteal phase, and are associated with development of oversized “persistent” dominant follicles (reviewed in Adams 1998). The oversized follicles, however, will not persist indefinitely and, after a prolonged growing phase, will enter a static phase followed eventually by regression and emergence of a new wave (Adams et al. 1992b). In this regard, low-level progesterone exposure (and therefore less inhibition of LH), at the time the dominant follicle normally stops growing, may be a fundamental component in the etiology of ovarian follicular cysts, consistent with early studies where low doses of exogenous progesterone were associated with follicular cyst formation in cattle, sheep and pigs (Adams et al. 1992b).

Lowered fertility subsequent to prolonged progestogen treatment (≥ 14 days) observed in early studies has been attributed to aging of the oocyte within the long-lived, oversized follicles (reviewed in Adams 1998). Spontaneous maturation (i.e., germinal vesicle breakdown and cumulus expansion) was evident in 23 of 23 “persistent” dominant follicles compared with 5 of 29 in growing dominant follicles (Revah et al. 1996). The potential of inducing “persistent,” oversized follicles for the purpose of synchronizing estrus has been investigated (Kinder et al. 1996), but is complicated by low fertility after ovulation of the aged oocyte.

**Estradiol & Progesterone**

Although the synchronizing effects of combined treatment with progestogen and estradiol have been known for decades, it was not until later discoveries of the effects of estradiol on dominant follicle regression that the reason for this effect was understood. In a series of studies (reviewed in Bo et al. 1995) estradiol treatment was found to suppress the growing phase of the dominant follicle, and suppression was more profound when given in combination with progesterone. The mechanism responsible for estrogen-induced suppression of follicle growth appears to be a systemic rather than a local effect, and involves suppression of FSH and LH (Bo et al. 2000). The combination of estradiol and progestogen was subsequently used to determine if suppression of follicle growth would induce new wave emergence at a consistent interval posttreatment regardless of the phase at which treatment is initiated. The interval from estradiol treatment to wave emergence in progestogen-treated cows was between 3 and 5 days (4.3 ± 0.2 days), and authors concluded that estradiol/progestogen treatment is a feasible approach to the synchronization of follicular waves among randomly cycling cows (Bo et al. 1995, 1996).

The use of estradiol/progestogen treatment for synchronization of estrus and ovulation has been revised by the addition of prostaglandin to ensure luteolysis and GnRH/LH or estradiol to synchronize ovulation. A typical protocol consists of insertion of an intravaginal progestin-releasing device and the administration of 2.5–5 mg estradiol-17β or 2 mg estradiol benzoate on Day 0 (to synchronize follicular wave emergence), and PGF at the time of removal of the progestin device (to ensure luteolysis) on Days 7 or 8. A low dose of estradiol (usually 1 mg) is given 24 hours after progestin removal, or GnRH 48 to 60 h after removal, to synchronize an LH surge (approximately 16 to 18 hours after treatment) and
ovulation (approximately 24–32 hours later; Martinez et al. 2005). Fixed-time AI is typically done 30–34 hours after GnRH or second estradiol treatment (Mapletoft et al. 2002; Martinez et al. 2005). The degree of synchrony achieved with estradiol/progestogen has made fixed-time artificial insemination feasible (Bridges et al. 1999; Martinez et al. 2000) and has improved the efficiency of embryo transfer programs (Bo, Adams et al. 1995; Mapletoft et al. 2003).

The use of natural or synthetic estrogens, however, has been the subject of considerable controversy in the cattle industry due to increasing concern about potential toxic and carcinogenic effects of steroid hormone use in food-producing animals (reviewed in Yapura et al. 2011). In the European Union, estradiol and other steroid hormones have been banned for use as growth promotants and for reproductive management in animals designated for human consumption, and New Zealand and Australia have banned the use of estrogens in lactating dairy animals. The use of estradiol as growth promotant is still permitted in the United States and Canada, but no commercial preparations are available for the purposes of reproductive management (Yapura et al. 2011).

**GnRH-based Protocols**

Gonadotropin-releasing hormone has been used widely since it first became available commercially in the 1970s as a treatment for follicular cysts (Drost & Thatcher 1992). The effects of GnRH on follicular dynamics have also been investigated (Macmillan et al. 1991) and treatment was found to induce ovulation or luteinization of the largest follicle present at the time of treatment. Consequently, a new follicular wave was recruited approximately 2 days later, and the new dominant follicle was sufficiently grown by 7 days posttreatment to be capable of ovulation after PGF treatment (Thatcher et al. 1993). A 10-day synchronization program involving a 6-day interval between GnRH and PGF treatment was used by others (Twagiramungu et al. 1995), and pregnancy rate was not different from that of untreated controls. In a series of studies, workers in Québec (Twagiramungu et al. 1995; Roy et al. 1996) proposed the use of a second GnRH treatment 36–48 hours after PGF treatment to ensure ovulation of the extant dominant follicle. They found that the second GnRH treatment improved the precision of ovulation and permitted fixed-time insemination without adversely affecting pregnancy rates.

The use of GnRH-based protocols have now become common for fixed-time AI in dairy (Pursley et al. 1995, 1997) and beef cattle (Geary et al. 2001) in the USA. The treatment protocol that utilizes GnRH and PGF for fixed-time AI in dairy cattle has been called “Ovsynch” (Pursley et al. 1995). A limitation of GnRH-based protocols, however, is that emergence of a new follicular wave is synchronized only if GnRH treatment causes ovulation (Martinez et al. 1999). Cattle in which GnRH was given between Days 1 and 4 or Days 13 and 17 of the cycle had lower pregnancy rates than at other times (20 vs. 50%, respectively; Thatcher et al. 2000). When GnRH is administered during metestrus (Days 1–4), the dominant follicle may not ovulate but rather undergo atresia at the approximate time that PGF is given. The dominant follicle of the second wave (Days 13–17) may also not ovulate in response to the first GnRH treatment, and in the absence of ovulation, endogenous PGF may cause luteolysis and ovulation before fixed-time AI, resulting in low pregnancy rates. Recent studies have shown that the first GnRH results in ovulation in only 44 to 54% of dairy cows (Bello et al. 2006; Colazo et al. 2009), 56% of beef heifers (Martinez et al. 1999) and 60% of beef cows (Small et al. 2009). If the first GnRH does not synchronize follicular wave emergence, ovulation following the second GnRH may be poorly synchronized (Martinez et al. 2002a),
resulting in disappointing pregnancy rates following fixed-time AI (Martinez et al. 2002b). In addition, 
~20% of heifers show estrus before the injection of PGF, dramatically reducing fertility to fixed-time AI 
(Colazo et al. 2004; Wiltbank 1997). Prevention of early ovulations by addition of a progestin-releasing 
device to a 7-day GnRH-based protocol improved pregnancy rates after fixed-time AI in heifers 
(Martinez et al. 2002a, 2002b) and cows (Lamb et al. 2001).

Combination Protocols

Most fixed-time AI protocols utilized in the USA today are variations of the Ovsynch protocol. Variations 
include pretreatment with PGF, inclusion of a progesterone-releasing intravaginal device, and 
modifications in the duration and timing of treatments and insemination. To minimize handling, 
particularly in beef cattle, fixed-time AI is often done at the same time as the second GnRH (often 
referred to as “Cosynch”) rather than 24 hours later (Geary et al. 2001). In recent years, the interval 
between PGF and the second GnRH treatment has been lengthened from 48 h to 56, 60 or even 66 h; a 
common protocol in dairy cattle is an interval of 56 h with insemination 10–12 h later.

“Presynchronization” with either one dose or two doses of PGF 14 days apart, and administration of the 
first GnRH treatment 12 or 14 days after the second PGF treatment has also been used to improve 
pregnancy rates (Bartolome et al. 2002; Moriera et al. 2001). The objective is to give GnRH treatment 
when cows are between Days 5 and 12 of the cycle. In one review (LeBlanc 2001), presynchronization 
with PGF increased the pregnancy rate by 11 to 13% in dairy cattle, and an interval of 11 days between 
the second PGF and the first GnRH resulted in a higher pregnancy rate than the previously used 14-day 
interval (Galvão et al. 2007). A double Ovsynch protocol has also been reported to improve pregnancy 
rates compared to a single Ovsynch (Wiltbank et al. 2012). Another approach is to palpate cattle before 
initiating the GnRH-based program; those with a functional CL are given PGF (and GnRH 14 days later) 
and those with a large ovarian follicle or corpus hemorrhagicum are given GnRH (and the GnRH-based 
program is started 8 days later; Bartolome et al. 2002).

To test the efficacy of a shorter protocol in beef cows (Bridges et al. 2008), a 5-day vs. 7-day 
interval between GnRH and PGF was compared, in combination with a progestin device. The second 
GnRH treatment and fixed-time insemination were done 12 h later in the 5-day vs. 7-day protocol (i.e., 
72 h vs. 60 h after PGF) to provide more time and gonadotropin support for the ovulatory follicle to 
mature. Pregnancy rates were 11% higher with the 5-day protocol (Bridges et al. 2008) and others have 
reported similar findings in dairy cattle (Santos et al. 2010). However, due to a shorter interval between 
the first GnRH and induction of luteolysis in the 5-day protocol, two doses of PGF 6 to 8 hours apart 
were necessary to induce complete regression of the GnRH-induced CL. In contrast, results of a recent 
study on beef heifers (Kasimanickam et al. 2012) showed that the pregnancy rate was 10.3% higher in 
heifers inseminated at 56 h vs. 72 h after PGF in a 5-day Cosynch protocol. In dairy heifers (Colazo et al. 
2011), the pregnancy rate did not differ between 5-day and 7-day Cosynch protocols using a single 
administration of PGF, and the use of the first GnRH treatment in the 5-day protocol did not increase the 
pregnancy rate compared to heifers not given the first GnRH treatment. Similarly, the first GnRH 
treatment was found to be of no benefit in a 5-day Co-synch protocol with progestin in dairy heifers 
(Lima et al. 2011), but the pregnancy rate was higher when GnRH treatment and AI were done at 72 h
after PGF than at 56 h. Additional research is needed to determine the effects of various modifications and in various groups of cattle (beef vs. dairy, heifer vs. cow).

OVARIAN SUPERSTIMULATION
The objective of ovarian superstimulatory treatment in cattle is to induce growth of multiple large follicles to obtain the maximum number of competent oocytes (for collection and in vitro fertilization) or viable embryos (after ovulation and in vivo fertilization). However, variability in the superstimulatory/superovulatory response of the donor animal has remained one of the most limiting factors to successful embryo production systems. Many reports have been published on dosage regimens and types of gonadotropin preparations for ovarian superstimulation, but the results of controlled prospective studies have revealed that the variability in superstimulatory response is associated primarily with i) the intrinsic number of follicles present at wave emergence within individuals, and ii) the status of follicular wave development at the time treatment is initiated.

Predictability of the Superstimulatory Response
The most important contributor to variation in the superstimulatory response is the intrinsic complement of follicles per wave among individual cows (Singh et al. 2004; Burns et al. 2005; Ireland et al. 2008). Perhaps the best example of this was a study where a beef herd (n = 141) was treated with estradiol and progesterone (1st synchronization) and ranked according to the number of follicles ≥ 2 mm at wave emergence to select the upper and lower 10% of the herd (Singh et al. 2004). The high-end and low-end groups were treated with FSH twice daily for 3 days after the second synchronization. High-end cows had a significantly greater number of follicles than low-end cows at the time of wave emergence after both the first and second synchronizations, and the numbers of follicles at successive wave emergence within individuals were positively correlated (Figure 3). Superstimulatory treatment resulted in more than double the number of large follicles in the high-end group than in the low-end group. Authors concluded that 1) the superstimulatory response can be predicted by the number of follicles ≥ 2 mm at wave emergence, and 2) the number of follicles at wave emergence is repeatable within individuals and can be predicted (r = 0.77; p = 0.0001; Figure 3). In practice, the superstimulatory response = 71% of the number of follicles present at time of wave emergence.

Selection of donors on the basis of antral follicle count at wave emergence would appear to be a valuable tool for minimizing variability and optimizing use of time and resources, including embryo recipients, but surprisingly little attention has been given to it. No reference was found in the scientific literature on the use of antral follicle count at wave emergence for commercial embryo production in cattle. The basis for such extreme variability in the complement of follicles among individuals is not clearly understood although contributing factors include age (Malhi et al. 2008) and inherited - genetic (Mali et al. 2006) or epigenetic (Evans et al. 2010) - characteristics.

Figure 3. Frequency distribution (left) of cows in a beef herd (line), and in the low-end (black bars) and high-end groups (white bars) based on the number of ≥ 2 mm follicle in both ovaries at wave emergence.

Caption: Low-end (n = 20) and high-end (n = 16) cows represented the top and bottom 10% of the herd ranked by number of follicles at wave emergence. Twenty-eight out of 36 selected cows were outside
the herd mean standard deviation (horizontal line). Number of follicles detected (right) at the emergence of the 1st (A) and 2nd (B) synchronized waves, and at the end of ovarian superstimulatory treatment (C) in the high-end group (white bars) and low-end group (black bars). A difference (p < 0.05) between high- and low-end groups is indicated by an asterisk (*). (Adapted from Singh et al. 2004)

**Synchronization of Follicle Wave Emergence for Superstimulation**

The conventional protocol of initiating ovarian superstimulation during mid-cycle, approximately 8 to 12 days after estrus, was arrived at empirically. Studies in which a lesser response to superstimulatory treatments initiated early in the estrous cycle (2 to 6 days after estrus) versus later (9 to 11 days after estrus) appeared to validate the convention (Goulding et al. 1990; Lindsell et al. 1986). The reason for the relative success of the conventional approach may be explained by what we now understand about follicle dynamics.

From the model depicted in Figure 1, we hypothesized that a greater superstimulatory response will result from treatment initiated before the subordinate follicles of a wave begin to regress (i.e., before selection of a dominant follicle). In an initial study designed to test this hypothesis (Adams et al. 1993), recombinant bFSH was given to heifers before the time of selection (Day 1, ovulation = Day 0), or after the time of selection (Day 5) of the dominant follicle of Wave 1. Significantly more ovulations were induced in the preselection treatment group. A subsequent study was done to determine if exogenous FSH given at the expected time of the endogenous wave-eliciting FSH surge has a positive effect on the superstimulatory response (Nasser et al. 1993). The endogenous surge in FSH was expected to peak 1 day before wave emergence, so superstimulatory treatments were initiated on Day -1, 0 (ovulation), 1, or 2 in the respective groups, which corresponds to the day before, the day of, and 1 or 2 days after emergence of Wave 1. Significantly more large follicles developed and significantly more ovulations were induced when treatment was initiated on Day -1 or Day 0 than when initiated later.
In a direct comparison between waves, results of another study (Adams et al. 1994) revealed no differences in the number of large follicles recruited, the number of ovulations induced, or the number of ova/embryos recovered in heifers in which superstimulation was initiated on the day of emergence of Wave 1 or Wave 2. Consistent with the previous study (Nasser et al. 1993), when treatment was initiated ≥ 1 day after wave emergence, the superstimulatory response was reduced. Why then, did the results of early studies show a greater response to treatment initiated later in the estrous cycle (9 to 11 days after estrus) versus earlier (2 to 6 days after estrus)? The reason is that “early” wasn’t early enough. Two to 6 days after estrus is equivalent to 1 to 5 days after wave emergence and encompasses the period of maximal follicle dominance (reflected by the nadir in endogenous FSH; Figure 1). Conversely, 9 to 11 days after estrus (8 to 10 days after ovulation) brackets the time of spontaneous wave emergence in 2- and 3-wave cycles (Figure 1). Several studies involving superstimulation initiated in the presence or absence of a dominant follicle, or in the presence of many small follicles (i.e., near wave emergence) have consistently demonstrated the suppressive effects of follicular dominance on the superstimulatory response (reviewed in Adams 1998). Collectively, data suggest that superovulation may be induced with equal efficacy when treatment is initiated during the first or second follicular waves, and that the superstimulatory response is enhanced if treatment is initiated at the time of wave emergence (before the time of selection).

Based on duration of the developmental phases of the dominant follicle in 2-wave and 3-wave interovulatory intervals (Figure 1), the probability at any given time that the dominant follicle is not functionally dominant (i.e., late-static or regressing phases) is approximately 30% (6 of 20 days) for 2-wave heifers and 35% (8 of 23 days) for 3-wave heifers. More importantly, only approximately 20% (4 or 5 days) of the estrous cycle is available for initiating treatment at the time of follicular wave emergence. Therefore, a majority (80%) of the estrous cycle is not conducive to an optimal superovulatory response. The necessity of waiting until mid-cycle to initiate superstimulatory treatment implies monitoring estrus and an obligatory delay. To obviate these problems, studies have been done to determine if superstimulation subsequent to elective induction of follicular wave emergence could be used with equal or greater efficacy than the conventional protocol.

One approach involved transvaginal ultrasound-guided follicle ablation, as described above, to synchronize wave emergence among heifers at random stages of the estrous cycle, followed by 400 mg Folltropin-V given as a single subcutaneous dose 1 day after ablation, and PGF 48 hours after Folltropin treatment (Bergfelt et al. 1997). Nonablated control heifers were given Folltropin 8 to 12 days after estrus and PGF 48 hours later. Combined over 2 experiments (Table 1), there was no difference in the superovulatory response between the ablated and nonablated groups. A similar approach was used in pubertal calves for the purpose of oocyte collection (Brogliatti et al. 1997). Transvaginal ultrasound-guided follicle ablation was used to synchronize wave emergence within a group of 7 month-old calves prior to superstimulation. Twice as many large follicles were available for aspiration and nearly twice as many oocytes were collected from calves that were given a superstimulatory dose of FSH before the time of selection of the dominant follicle compared with those treated after selection.

A second approach involved treatment with 5 mg estradiol-17β 1 day after insertion of a progestogen implant, as described above, followed by 400 mg Folltropin-V given as a single or multiple dose beginning 5 days after implant insertion (Bo et al. 1996). PGF was given 48 hours after Folltropin
treatment was initiated and the progestogen implant was removed 12 hours after PGF treatment. Control heifers were given the same dose of Follitropin between 8 and 12 days after estrus. Combined over 2 experiments (Table 1), the superovulatory response was equivalent or better in the steroid-treated group than that of the control group.

**Table 1. Superovulatory response of control heifers treated between 8 and 12 days after estrus compared with that of heifers superstimulated after synchronization of wave emergence by follicle ablation (Bergfelt et al. 1997) or progestogen + estradiol treatment (Bo et al. 1996).**

<table>
<thead>
<tr>
<th>Ablation study</th>
<th>Steroid-treatment study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>No. of heifers</td>
<td>35</td>
</tr>
<tr>
<td>CL</td>
<td>22.9</td>
</tr>
<tr>
<td>Total ova/embryos</td>
<td>10.1</td>
</tr>
<tr>
<td>Fertilized ova</td>
<td>7.3</td>
</tr>
<tr>
<td>Transferable embryos</td>
<td>5.4</td>
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A third alternative is to use GnRH to induce ovulation of the dominant follicle, which would be followed by wave emergence 1 to 2 days later. However, as indicated earlier, emergence of a new follicular wave was synchronized only when treatment caused ovulation. Without presynchronization, the first GnRH treatment results in ovulation in less than 60% of animals (Martinez et al. 1999; Small et al. 2009). Not surprisingly, treatment with GnRH at random stages of the estrous cycle, prior to initiating superstimulatory treatments, resulted in lower superovulatory responses than treatments initiated after follicular aspiration or estradiol (Deyo et al. 2001). In another study (Wock et al. 2008), progestin-treated dairy cows (n = 411) were superstimulated 4 days after estradiol treatment or 2 days after GnRH treatment, and no difference in the number of transferable embryos between groups was detected. In a retrospective analysis of commercial data (Steel & Hasler 2009), dairy donors superstimulated 60 hours after the administration of GnRH (n = 245) produced a similar number of transferable embryos as those superstimulated 4 days after estradiol treatment (n = 691). Controlled studies with the use of GnRH must be conducted to validate these promising results.

Collectively, these studies demonstrate that elective induction of follicle wave emergence offers the advantage of initiating superstimulatory treatment forthwith, or at a time that is both convenient for the practitioner and optimal for follicle recruitment. Thus, the full extent of the estrous cycle is available for superstimulation and the need for detecting estrus or ovulation and waiting 8 to 12 days to initiate treatment is eliminated.

**Role of Progesterone in Superovulatory Treatment**

Surprisingly, little attention has been given to the role of progesterone before or during superstimulatory treatment. Protocols based on synchronized wave emergence commonly include co-treatment with progesterone, presumably because conventional superstimulatory protocols are initiated during mid-diestrus. Other than to prevent premature ovulation, the necessity of progesterone before or during treatment remains unclear. Although no differences were detected in the previously cited study between Wave 1 (low progesterone) and Wave 2 (high progesterone) (Adams et al. 1994),
results of a recent study in Nelore (Bos indicus) donors raise some interesting questions about the role of progesterone before or during FSH treatments (Nasser et al. 2011). Superstimulatory treatment was initiated, with or without an intravaginal progesterone-releasing device, at the time of ovulation (emergence of the first follicular wave) that had been synchronized by estradiol treatment followed by insertion of an intravaginal progesterone-releasing device for 9 days. Although the superovulatory response and the total number of ova/embryos collected did not differ between groups, the number of transferable embryos was reduced in cows superstimulated without the use of a progesterone device (Nasser et al. 2011). However, the experimental design induced an artificially prolonged period of low progesterone in the group in which progesterone was not given during superstimulation (i.e., >2 weeks), and results may be attributed to an alteration in the hormonal milieu of the tubular genitalia at the time of insemination. Similarly, in a recent study comparing the superstimulatory response of Wave 1 vs. Wave 2 in early postpartum (33 days) dairy cows (Rivera et al. 2011), there was no difference between groups in the number of ova/embryos or transferable embryos collected per cow, but the proportion of the total that were transferable was greater in the Wave 2 group. Again, the experimental design approximated Waves 1 and 2 by artificial synchronization with GnRH and progesterone, and was not designed to determine if the effect was on oocyte competence or related to hormonal priming of the tubular genitalia. Dairy cows with a postpartum anovulatory period of >20 days commonly have a short first cycle (<14 days) with a small short-lived CL and low circulating progesterone concentrations (reviewed in Adams 1999). Hence, a proportion of the cows in the Wave 1 group likely experienced a prolonged period of low progesterone that the Wave 2 group did not, as a result of pretreatment of the Wave 2 group with exogenous progesterone (Rivera et al. 2011).

**Extended Superstimulatory Treatment**

Results of a careful study of follicle dynamics revealed that follicles as small as 1 mm respond to periodic surges in FSH and are part of each follicular wave that is elicited by endogenous FSH surges (Figure 4; Jaiswal et al. 2004). At wave emergence, all follicles of the wave are dependent on FSH for continued development, and as the endogenous FSH surge begins to subside, subordinate follicles begin to regress, starting with the smallest of the wave (Figure 4; reviewed in Adams et al. 2008). Exogenous FSH in superstimulatory protocols is intended to prevent the drop in circulating FSH concentrations and thereby rescue the follicles of that wave from atresia (Adams et al. 1993). While conventional 4- or 5-day FSH treatment enables follicles that are ≥4 mm at the start of treatment to reach ovulatory size, it may not be sufficiently long to enable 1 to 3 mm follicles to reach ovulatory size. Assuming a growth rate of 1 to 2 mm per day, 4 mm follicles will require about 4 days to reach a diameter of ≥10 mm, whereas follicles that are 1 mm will require an additional 2 to 3 days of FSH support.

Results of a recent study support the concept of prolonging superstimulatory treatment to rescue more follicles of the wave (Garcia Guerra et al. 2012). Lengthening the FSH treatment protocol from 4 to 7 days, without increasing the total amount of FSH administered, increased the number of ovulations and the synchrony of ovulations, and tended to increase the mean numbers of total ova/embryos, fertilized ova, and transferable embryos recovered. It was concluded that traditional 4-day superstimulatory treatment protocols may not provide adequate time for all follicles within the cohort
to acquire the capacity to ovulate, and that prolonging FSH treatment to 7 days provided additional time for smaller follicles of a wave to reach an ovulatory size and acquire the capacity to ovulate.

**Figure 4. Ovarian follicular wave pattern detected in follicles as small as 1 mm in diameter (2-wave pattern shown)**

Caption: Small follicles (1 to 3 mm) in parentheses illustrate wave emergence 2.5 d earlier than previously detected (shaded bars). Note that the growth rate is similar among follicles of the wave (dotted lines) until FSH begins to decline, at which time growth rate slows and regression begins starting with the smallest follicles of the wave.

**SUMMARY AND CONCLUSIONS**

Wave-like follicle development in cattle is manifest as simultaneous emergence of a group of small (i.e., 1 mm) follicles in both ovaries in response to a surge in circulating concentrations of FSH. The largest of the group at its earliest detection (1 mm) usually remains dominant (random distribution in either left or right ovary), but individual follicle growth rates are similar until FSH drops. The vast majority of estrous cycles are composed of two or three follicular waves. Two-wave cycles are consistently shorter (19–20 d) than 3-wave cycles (22–23 d). The number of follicles recruited into each wave varies greatly among individuals, but is highly repeatable within individuals. Variability in response has continued to be one of the most frustrating problems in synchronization and superovulation programs in cattle. Antral follicle counts at wave emergence are predictive of the superstimulatory response, and incorporation of techniques designed to control both luteal and follicular wave dynamics reduce the variability and improve the response by taking advantage of endogenous rhythms. New synchronization schemes provide the convenience of being able to initiate treatment quickly and at a self-appointed time, without sacrificing response.
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Something Old, Something New: Advances in Diagnosing Respiratory Disease in Feedlot Cattle
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INTRODUCTION
Bovine respiratory disease (BRD) is a leading cause of animal morbidity and mortality in the early feedlot period in beef cattle. Within the first month after arrival, 20–60% or more of weanling calves entering the feedlot may be affected by viral and/or bacterial pneumonia. Cattle with BRD show reduced daily gains, carcass quality, and prolonged days on feed compared with those that do not require treatment for BRD. The impact of BRD on beef production is widely recognized, and it remains a leading cause of economic loss to the industry. As such, there has been tremendous investment by the beef industry to support research into methods of BRD prevention and treatment, in an effort to mitigate such financial losses. However, BRD remains a challenging diagnosis to confirm - our ability to detect affected calves in a timely fashion, or to accurately establish that their clinical signs are truly attributable to BRD, remains suboptimal. Without accurate detection methods, valid assessment of preventative and therapeutic measures is difficult, since the allocation of calves to sick versus healthy groups for the comparison of various interventions is compromised. This review explores the effectiveness of current methods to detect BRD in feedlot cattle, and identifies emerging technologies that may be incorporated into the feedlot setting to more accurately diagnose respiratory disease in feedlot cattle.

As examples of the challenge in diagnosing BRD, several studies have compared clinical diagnosis of BRD (i.e., treatment for BRD as determined by feedlot records) to retrospectively classifying BRD-cattle based on the presence of lung lesions at the time of slaughter. Wittum et al. (1996) showed that 72% of all cattle in their study had lung lesions present at the time of slaughter, whereas only 35% of the cattle had received treatment for BRD at some time between birth and slaughter. Looking at animal growth, treatment for respiratory disease either prior to weaning or during the feedlot period was not correlated with average daily weight gain (ADG). However, the presence of lung lesions at slaughter was negatively correlated with ADG; cattle with lung lesions at slaughter gained 0.076 kg less per day than animals with no lung lesions (p < 0.01). Thompson et al. (2006) similarly found that 43% of cattle had lung lesions at slaughter despite only 23% being clinically detected and treated during the feedlot period. In contrast, Gardner and colleagues (1999) detected lung lesions in 33% of cattle at slaughter, in comparison with a clinical BRD treatment rate of 50%. Both Thompson and Gardner demonstrated that the presence of lung lesions at slaughter correlated with reduced daily gain, and Gardner’s study also showed that lung lesions at slaughter were correlated with reduced hot carcass weights and carcass quality. From these studies, it is evident that BRD has impact on animal wellbeing and growth, but that treatment for clinical BRD during the feeding period is not a reliable indicator of BRD within the herd, since many cattle with lung lesions at slaughter remain undetected clinically, and some cattle may be treated for BRD that are actually not affected. Unfortunately, while slaughter diagnosis of BRD is useful to survey the effectiveness of preventative and treatment measures in feedlot management over time, this method of diagnosis lacks clinical usefulness for the individual animal, since it does not detect cases in real-time for the purposes of intervening and having an impact on health and performance. The ability to detect BRD clinically (and subclinically) remains the goal for feedlot producers and veterinarians, in order to effectively treat respiratory disease, reduce animal suffering, and optimize preventative and therapeutic use of antibiotics in beef cattle.

The reality of clinically diagnosing BRD lies with the fact that large numbers of cattle, housed together, must be checked daily for early detection of BRD to occur. Criteria used to assess these cattle are defined by cost, labour, and time, as well as minimizing risk to the cattle during assessment. More
specifically, it is not feasible to move cattle daily from their home pen to be restrained in a chute for assessment purposes, as this would be labour intensive, time consuming, and would impose stress and increased potential for injury to the animal during frequent restraint. It is evident that effective detection of BRD needs to therefore occur in the home pen. This has been traditionally done through “pen checkers” that ride each pen at least daily, to observe the group of cattle for any animals displaying atypical behaviour: for example, dull mentation, not remaining with the herd mates, being slow to respond when approached, and reduced appetite. The latter can be assessed best at feeding times, when bunks are being filled. Any calf that does not move to the bunks in response to the feed truck is likely to be clinically ill and requires further assessment. However, an additional measure of reduced appetite is poor rumen fill, as determined by a gaunt appearance over the left paralumbar fossa. Cattle that are flagged as potentially being sick using these criteria are then pulled from the home pen and further examined in a chute. An abbreviated clinical examination is performed on any pulls, typically including measurement of rectal temperature and visualization of the animal for additional respiratory signs such as nasal discharge or cough, versus signs that may attribute illness to an alternate body system. Most commonly, a decision to treat for BRD is ultimately dictated by the presence of fever (rectal temperature of 40.0°C or greater) in pulled animals.

How effective is this method at detecting BRD? We recognize that it is entirely reliant on the skill of the pen checkers to detect and pull the appropriate animals for further assessment. Skilful pen checkers require knowledge of normal cattle behaviour and relevant clinical signs to look for in affected cattle, they must have adequate time to assess all animals in the pen in a systematic fashion, and they should possess a degree of instinct to also pull those cattle which fall outside the prescribed abnormal criteria but still appear “not quite right.” Examples of factors that may reduce the effectiveness of pen checking include time constraints during busy feedlot periods (such as processing at entry), distraction, inadequate training or knowledge of normal cattle behaviour, and abnormal behaviour demonstrated by calves that are stressed from recent weaning.

Beyond pulling the appropriate cattle from the home pen, there are limitations to the second tier of assessment in the chute by the hospital crew. Not all cattle with clinically significant BRD have an elevated rectal temperature at the time of assessment, and often more severely affected cattle will have normal or subnormal temperatures as they become systemically compromised. Other signs of respiratory disease, such as alterations in the rate or character of breathing, are frequently affected by the stress and change in behaviour of cattle when they are separated from the group and restrained in a chute system.

An early study assessed the sensitivity and specificity of pen checkers and hospital crew to detect BRD in a feedlot setting. Salman and colleagues (1988) followed a cohort of cattle from entry into a feedlot until slaughter, and compared the ability of the pull crew to detect BRD (defined as being pulled from the home pen for assessment in the chute) with that of the hospital crew (BRD defined as being treated after determination of rectal temperature). The gold standard diagnosis was BRD as diagnosed by a veterinarian performing a clinical examination. The pull crew had the same sensitivity (94%) in detecting BRD as the hospital crew, but slightly less specificity (77%) compared with the hospital crew (81%). This study suggested that pen checking is a reasonably good method to detect BRD, and that confirmation of diagnosis is mildly improved by further clinical assessment of cattle in the chute. The conclusions of this study were limited by the very low incidence of BRD seen in the cohort of cattle studied, however.

Recent efforts to improve the identification of suspect animals to pull for further examination focus on removing the human element from this process, namely through automated surveillance of cattle within their home pen. Buhman and colleagues (2000) monitored feed (presence at the feed bunk) and water activity of cattle using automated head gates and individual animal identification. Clinical BRD was associated with increased drinking frequency in the first 4–5 days after arrival at the
feedlot, and reduced feed/water activities during the period of peak BRD cases (11–27 days post-arrival). This suggested that automated data capture on individual animal appetite and water consumption may be a substitute for human observation of the group during feeding times, and presents a real-time continuous electronic method to detect animals that begin to vary from their normal habits. Similarly, changes in behavioural parameters of cattle have been tracked using accelerometers and pedometers (Hanzlicek et al. 2010). In this study, reduced steps taken and increased time spent lying down were associated with onset of clinical illness in cattle that were experimentally infected with Mannheimia haemolytica, a common bacterial cause of bovine pneumonia. These outcome measures would be difficult for a pen crew to determine, given that cattle behaviour is altered by the stress associated with presence of the pen checker and that their observations are limited to brief points in time. Thus computer monitoring of animal activity may be more reliable in detecting abnormal animal behaviour.

Measurement of rectal temperature at a point in time (during assessment in the chute after being pulled from the home pen) can be affected by stage of disease, diurnal variation in core body temperature, and hyperthermia associated with animal resistance to handling. Ideally, continuous measurement of core body temperature of all animals would more reliably detect those with BRD that is subclinical or masked by animal stress in the presence of humans (Timsit et al. 2011). Several investigators have recently demonstrated that temperature can be monitored non-invasively in the home pen. Rose-Dye and colleagues (2011) utilized an indwelling intraruminal thermometer to remotely track body temperature in cattle experimentally infected with viral or bacterial pathogens. Temperatures determined by the intraruminal thermometer correlated well with rectal temperature, indicating that rumen temperature can be used as a surrogate measure of body temperature and changes associated with disease. Placement of intraruminal thermometers to all cattle in a feedlot setting would be associated with increased costs of equipment, labour and pose slight risk to the cattle during ororuminal administration of the thermometer. Therefore, another innovative method to detect body temperature of cattle has been the use of infrared thermography. Schaefer and colleagues have demonstrated that body temperature can be monitored by determination of the radiant thermal profile of the eye and surrounding orbital structures in cattle (2007). By positioning the thermography camera at the pen watering stations, it has been possible to remotely track body temperature of feedlot cattle over time (Schaefer et al. 2012). This has the advantage of tracking and electronically capturing each individual animal’s temperature over various periods of the day, and was demonstrated to detect early changes in temperature ahead of clinical onset of BRD (Schaefer et al. 2007). With refinement of the above-mentioned technologies, it is likely that animal health surveillance can be applied to all animals and be done within the home pen on a continuous basis over the feeder period. Integrating several of these measures, such as feed/watering activity and body temperature, into computer algorithms in parallel may inform producers in real-time of animals that require immediate assessment. The currently employed radiofrequency identification (RFID) ear tags may be linked with a global positioning system (GPS) to find suspect animals in the home pen when the computer algorithm has flagged them as potentially sick and requiring examination. This may potentially result in earlier treatment in the course of respiratory infection and thereby improve clinical outcomes.

Once a suspect animal is pulled for further examination, clinical diagnosis of BRD is strengthened by use of a clinical score that encompasses consideration of more than just the rectal temperature. Over time, research studies of BRD have evolved weighted scoring systems that improve diagnosis by assessment beyond rectal temperature, including scoring of mentation, appetite, and presence of respiratory signs such as nasal or ocular discharge, cough, or altered respiratory rate or character. Through incorporation of these parameters into a weighted scoring system, clinical confirmation of BRD in cattle pulled from their home pen for further examination may be improved (Schaefer et al. 2007; Lekeux 2002; Poulsen et al. 2009).
Ancillary tests that have been evaluated to augment the clinical examination include hematology, lactate concentration, measurement of acute phase proteins in blood, airway sampling, and diagnostic imaging modalities. Total white blood cell count and differential cell count values are highly dependent on the stage of disease, resulting in leukopenia initially followed by leukocytosis as the inflammatory response progresses. As such, hematology is poorly predictive of disease or severity of infection within an animal. Similarly, blood lactate concentration has been unreliable in differentiating healthy cattle from those with BRD (Hanzlíček et al. 2010), except when BRD is severe, in which case an elevated blood lactate (> 4 mmol/L) was a sensitive and specific predictor of impending death in the subsequent 24 hour period (Coghe et al. 2000).

In cattle, predominant acute phase proteins that increase in response to inflammation include haptoglobin, fibrinogen, lipopolysaccharide A, and serum amyloid A. Of these, serum haptoglobin is the most robust indicator of inflammation to differentiate sick versus healthy calves. Godson and colleagues (1996) and Ganheim et al. (2003) each demonstrated that haptoglobin concentration significantly rises within 24 hours of the onset of bacterial infection. In contrast, viral infection yields a rise in haptoglobin approximately 5 days postinfection, representing the onset of fever after a period of incubation of the virus. Each acute phase protein contributes differently to the inflammatory response, and therefore time to peak concentration varies with the protein measured. The measurement of two or more acute phase proteins simultaneously may best detect BRD in the feedlot setting when time of infection is unknown. For example, in a study of acute phase protein changes associated with BRD, sensitivity and specificity of acute phase proteins to detect BRD was optimized when serum haptoglobin and fibrinogen concentrations were used in parallel to reach a diagnosis (Humblet et al. 2004).

Airway sampling to confirm a diagnosis of BRD may be done by transtracheal aspirate, bronchoalveolar lavage, or deep nasopharyngeal swab. The benefit of these samples is that pathogen(s) causing the respiratory signs may be identified to better target treatment options or to develop an appropriate preventative health plan for the remaining herd mates. Bacterial culture of airway samples should be performed on multiple animals at varying stages of disease, and the results should be interpreted as a group-level diagnostic tool, because false positive culture results may be obtained from some animals since the bacterial pathogens of BRD are also commensal organisms of the upper respiratory tract of cattle. Transtracheal aspirate and bronchoalveolar lavage are invasive sampling methods and are not easily performed under feedlot conditions. As such, less invasive methods to sample the airways have been recently investigated. These include the collection of exhaled breath to measure constituents within the breath that may reflect lung inflammation. Leukotriene B4 and nitric oxide were altered with lung inflammation (Reinhold et al. 2000; Roller et al. 2007). Investigation into other constituents in the exhaled breath that may be more robust measures of lung inflammation are ongoing, as this method to collect airway samples is non-invasive, generally simple to perform, and is met by limited resistance from calves during the sampling period (Hewson, unpublished observations).

Diagnostic imaging of the chest may include ultrasonography and radiography. In a feedlot environment, the utility of radiography is limited by the cost of equipment and increased radiation exposure to feedlot personnel when evaluating large numbers of cattle during outbreaks. Ultrasound examination of the thorax to detect lung consolidation, pleural roughening, or pleural effusion, is more feasible to accomplish in the feedlot. Several recent publications have evaluated the utility of ultrasonography to detect BRD in feedlot cattle. In an experimental challenge study with Pasteurella multocida, abnormalities of the lung detected by ultrasonography correlated well with the severity of lesions on subsequent necropsy examination (Reinhold et al. 2002). Pulmonary changes are detectable by ultrasound within hours following bacterial infection of cattle (Ollivett et al. unpublished data). However, Abutarbush and colleagues tracked lung lesions over time by ultrasound imaging of the right hemithorax, and were not able to identify correlation between ultrasound findings and clinical outcome.
in feedlot cattle (2012). Whether improved correlation would be found with ultrasonography of the entire lung field bilaterally is not currently known. More work is needed to determine the sensitivity and specificity of thoracic ultrasonography as a screening modality. The diagnostic advantage to ultrasonography may be the improved ability to confirm the development of pneumonia early in the course of disease when a calf is pulled for further examination based on home pen surveillance methods. Confirmation of lung lesions may prompt treatment of such animals despite a lack of fever, allowing for earlier treatment when therapeutic interventions are more likely to be effective.

**CONCLUSIONS**

Diagnosing BRD in feedlot cattle involves skilled identification of animals displaying abnormal behaviour within the home pen, and subsequently pulling these cattle for more detailed assessment by clinical examination while restrained in a chute. Limitations to this process exist and are demonstrated by lack of correlation between clinical diagnosis of BRD and the presence of lung lesions at slaughter. To improve case detection, it is critical that priority is given to the process of pen checking, that personnel understand the essential role that it plays in early detection of disease, and that the process is monitored for efficacy on a regular basis. Inadequate pen checking and failing to pull all suspect animals can lead to significant production losses in the feedlot setting. As technology advances, it is becoming increasingly possible to improve our detection of BRD-affected cattle within the home pen through the use of remotely monitored measures of disease such as behavioural changes and body temperature. Use of two or more parameters in parallel, and creation of appropriate computer algorithms to define cases as suspect, will likely enhance our ability to achieve early and more accurate diagnosis of BRD. With improved case detection, research into preventative and therapeutic measures will also ultimately be improved, through more reliable allocation of cattle into “sick” versus “well” groups.

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Managing the Collateral Damage of Inflammation to Optimize Outcome in Cattle with Respiratory Disease

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INTRODUCTION
Historically, treatment of Bovine Respiratory Disease (BRD) has been limited to administration of antibiotics. Research efforts have centered on improving the efficacy of antimicrobials used, as well as optimizing labour and minimizing impacts of treatment on carcass quality. More recently, there has been growing recognition that inflammation plays a key role in the lung lesions that occur in BRD. Therefore, there is currently much interest in modification of the host inflammatory response through antinflammatory therapy, in an attempt to reduce the impact of infection on the development of lung lesions and ultimately on feedlot performance.

THE HOST INFLAMMATORY RESPONSE IN BRD
Infection of the lung with *M. haemolytica* initiates a cascade of inflammatory events that involves close interaction between endothelial activation, recruitment of inflammatory leukocytes, and triggering of complement and coagulative pathways. This complex response is orchestrated by pulmonary intravascular (Singh et al. 2004) and alveolar macrophages, but also involves respiratory epithelial and endothelial cells, neutrophils, lymphocytes, mast cells, platelets, and local nerve fibers.

The release of multiple chemokines, but in particular IL-8, results in the massive influx of neutrophils into infected tissue early in the course of *M. haemolytica* pneumonia. Walker et al. (1985) demonstrated that neutrophil recruitment to the lung occurs as early as 30 minutes following experimental exposure to aerosolized *M. haemolytica*, with significant neutrophil influx detectable by 60–120 minutes postinfection. Neutrophils are essential to the containment of infection, through the release of additional proinflammatory mediators, degranulation to release preformed proteolytic enzymes and antibacterial compounds (defensins, acid phosphatase, lactoferrin, and lysozyme), and the liberation of oxidative free radicals. These functions of neutrophils are fundamental to bacterial killing. Tissue injury secondary to neutrophil influx is a result of excessive free radical generation and enzyme release, leading to “bystander” injury of local lung parenchyma.

THE IMPORTANCE OF NEUTROPHILS TO THE PATHOGENESIS OF LUNG LESIONS
Slocombe et al. (1985) demonstrated the importance of neutrophils in the pathogenesis of pulmonary lesions in acute pasteurellosis. In calves with normal neutrophil numbers prior to infection, clinical changes were observed following inoculation with *M. haemolytica*, and necrotizing bronchopneumonia was evident on gross and histological assessment of lung tissue from these calves. In contrast, neutrophil-depleted calves remained asymptomatic following inoculation, and showed drastically reduced gross and histopathological lung lesions. Minimal lung lesions, limited to atelectasis and septal edema, were similarly reported in neutropenic calves challenged intrabronchially with *M. haemolytica* (Weiss et al. 1991). Thus, parenchymal necrosis and hemorrhage associated with *M. haemolytica* infection appear to be caused by neutrophil-dependent mechanisms, whereas increased vascular permeability appears to involve both neutrophil-dependent and neutrophil-independent mechanisms.

MODULATION OF THE HOST INFLAMMATORY RESPONSE
Recognizing the role of neutrophilic influx in the development of lung lesions, there has been increasing interest in modulation of the host inflammatory response in the treatment of BRD. Efforts to reduce lung lesions can be divided into two main approaches: upregulation of the host immune response to
facilitate effective clearance of bacteria, or downregulation of exuberant host inflammatory response to reduce neutrophil-mediated tissue injury. In the former approach, prior treatment with G-CSF or IL-8 has been used, for example, in an attempt to prime neutrophil functions such as oxidative burst and phagocytic activity (Mitchell et al. 2003). In contrast, treatments to downregulate the inflammatory response and thereby decrease neutrophil-mediated tissue injury have investigated select antibiotic classes, as well as both nonsteroidal and steroidal antiinflammatory drugs. A survey of producer treatments of BRD demonstrated that many producers utilize such ancillary therapies in addition to antimicrobial treatment, with 22% using a corticosteroid, 41% using an NSAID, and 33% using an antihistamine in addition to an antibiotic to manage BRD (USDA 2001).

a) Antiinflammatory Effects of Antibiotics
Researchers have become increasingly aware of the potential role of certain antibiotics in controlling inflammation. In particular, antiinflammatory benefits of macrolides have received considerable attention. Pretreatment with tilmicosin prior to experimental infection of calves with *M. haemolytica* resulted in reduced pulmonary inflammation as assessed by BAL cytology (Chin et al. 1998). Further, tilmicosin treatment following infection significantly reduced the extent of gross lung lesions by 72 hours postinoculation with *M. haemolytica* compared to saline-treated control calves (Goubau et al. 2000). Although tilmicosin did not affect initial neutrophil infiltration to the site of infection or neutrophil oxidative and phagocytic capacity, it enhanced neutrophil apoptosis in treated calves as compared to neutrophils of sham-treated calves in the study by Chin et al. (1998). This effect was independent of the presence of *M. haemolytica* and appears to involve induction of apoptosis of neutrophils for macrophage clearance through phagocytosis rather than neutrophil lysis (Chin et al. 2000). Tilmicosin also inhibits the proinflammatory cascade by modulating macrophage response to inflammatory stimuli (Lakritz et al. 2002). Similar antiinflammatory and proresolution benefits have recently been reported for tulathromycin, which also acts dually on neutrophils and alveolar macrophages (Fischer et al. 2011; Fischer et al. 2013).

b) Antiinflammatory Effects of Nonsteroidal Antiinflammatory Drugs (NSAIDs)
Various studies have investigated the effects of immune regulation by cyclooxygenase (COX) inhibitors to prevent prostaglandin and thromboxane synthesis. In comparison with treatment by antibiotics alone, faster clinical resolution of disease (fever, decreased appetite) or fewer lung lesions detected at slaughter occurred when cattle with BRD were treated with antimicrobials in combination with meloxicam (Bednarek et al. 2003; Friton et al. 2005), flunixin meglumine (Lockwood et al. 2003; Guzel et al. 2010), ketoprofen (Lockwood et al. 2003; Sabate et al. 2004), carprofen (Lockwood et al. 2003; Elitok and Elitok, 2004), or diclofenac sodium (Guzel et al. 2010). With regard to the long-term effects of NSAID treatment on feedlot performance, improved ADG and overall gain are achieved when cattle with BRD are treated with meloxicam in addition to florfenicol or oxytetracycline (Bardella et al. 2002; Friton et al. 2005). In contrast, ADG over 35 days did not differ when flunixin was combined with tilmicosin in the treatment of cattle with BRD (Hellwig et al. 1999). Treatment with a product of florfenicol combined with flunixin reportedly results in no benefit to ADG, body weight or mortality rate in cattle with BRD, compared with treatment with either tulathromycin or ceftiofur alone (Hannon et al. 2009; Van Donkersgoed et al. 2009). However, these studies lacked a treatment group of florfenicol alone, and thus the additional impact of NSAID treatment relative to that of antimicrobial treatment alone could not be determined.

ANTIINFLAMMATORY EFFECTS OF GLUCOCORTICOIDS
Glucocorticoids modulate immune function by altering transcription of proinflammatory and adherence proteins. Phospholipase A2 inhibition by corticosteroids reduces the production of arachidonic acid
metabolites and PAF, which are involved in chemoattraction of neutrophils into infected tissue and subsequent neutrophil activation.

Corticosteroids have yielded variable success in the treatment of BRD. Immunosuppressive doses of dexamethasone in one study (Christie et al. 1977) resulted in poorer response to treatment with oxytetracycline and higher relapse rates than those seen in cattle treated with oxytetracycline alone. Similarly, prior treatment with dexamethasone resulted in more extensive and severe lung lesions in an experimental model of Haemophilus somnus infection in calves (Jackson et al. 1987). In contrast, experimental studies of M haemolytica pneumonia have shown equivocal outcomes or clinical benefits of treatment during the acute period of infection when antimicrobials were combined with flumethasone (Sustronck et al. 1997; Bednarek et al. 2003), dexamethasone (Moire et al. 2002; Malazdrewich et al. 2004), or methylprednisolone acetate (Espinasse et al. 1992). The clinical efficacy of isoflupredone acetate administered in combination with oxytetracycline on feed intake and weight gain was evaluated using an experimental model of Mannheimia haemolytica infection (Hewson et al. 2011). Experimental infection caused a reduction in dry-matter intake and average daily gain (ADG) in heifers that received no treatment. Oxytetracycline treatment alone did not prevent reduction in feed intake and ADG during the acute infection period, whereas combined treatment of oxytetracycline with isoflupredone acetate attenuated these effects. The combined treatment also resulted in faster clinical improvement. No significant differences were evident between the oxytetracycline and oxytetracycline-isoflupredone groups with respect to dry matter intake or ADG throughout the 12-week study period.

Based on the existing literature, it is currently still not possible to fully determine whether corticosteroids have a clinical application in managing BRD. Differences in treatment outcomes between the limited corticosteroids that have been studied thus far may reflect the method used for BRD diagnosis in the feedlot setting, timing of medical intervention with respect to onset of infection, involvement of multiple respiratory pathogens in naturally occurring respiratory disease, or simply effects specific to the corticosteroids used.

**EVIDENCE-BASED MEDICINE in BRD**

Many of the past research studies assessing the use of ancillary antiinflammatory treatments to manage BRD have been short-term studies utilizing an experimentally induced disease model. Experimental models of infection have an advantage over studies of naturally occurring disease, in which the major limitation to assessment of treatment efficacy is the correct assignment of cattle to BRD-affected or unaffected groups. This limitation has been emphasized in another proceedings here (Hewson 2013), discussing the perils of clinically diagnosing BRD under feedlot conditions. Experimental infection models increase the confidence that treatments are applied appropriately to truly sick animals, allowing for a more reliable determination of the impact of various treatment interventions. However, a recognized limitation to experimental models is that treatments are being evaluated without the multifactorial interplay between the host, pathogen(s) and environment that is seen when naturally occurring BRD develops. As such, the true efficacy of ancillary treatments needs to also be validated under field conditions. A recent analysis of the literature demonstrated that such evidence of field efficacy is lacking, with only 15 papers over a 44-year period being field studies that utilized appropriate study design and analysis to enable valid assessment of ancillary therapies in managing naturally occurring BRD in feedlot cattle (Francoz et al. 2012). Many of these studies also were restricted to the acute period of infection, and did not allow for determination of the long-term consequences of treatment on feedlot performance parameters. Of the 15 studies reported, 14 assessed the efficacy of antiinflammatory therapies (12 NSAIDs, 1 steroid, 1 both) and 1 paper assessed the utility of an immunomodulator in the management of BRD. Based on this scant literature to evaluate ancillary treatments of BRD under conditions of naturally occurring disease, it is difficult at present to draw firm conclusions as to their clinical application in the feedlot.
There is also the notion to consider that not every ancillary therapy is appropriate in every BRD-affected animal. There are those cattle where bronchopneumonia is effectively resolved by the host immune system without requiring any treatment, those cattle where routine antimicrobial therapy effectively clears infection with no residual long-term impact on lung morphology, function and feedlot performance, and then there are other cattle where infection would progress unchecked were it not for therapeutic intervention with both antimicrobials and antiinflammatory medication. Finally, some cattle have such severe lung lesions that they have a poor prognosis for survival regardless of treatment. The skill lies in adequately triaging BRD-affected cattle into these various subcategories, such that treatment decisions optimize good health outcomes while minimizing treatment costs in hopeless cases (Lekeux 2002). Use of serum haptoglobin and fibrinogen concentrations in parallel has been demonstrated as a sensitive method to screen cattle for those requiring additional NSAID therapy (Humblet et al. 2004). Likewise, blood lactate concentration is useful to predict impending mortality (Coghe et al. 2000) as an aid to feedlot veterinarians in determining which animals warrant euthanasia rather than pursuing extensive treatment of BRD.

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Respiratory Disease in Calves and its Impact on Future Productivity in the Dairy and Beef Industries

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INTRODUCTION
While the economic impact of bovine respiratory disease (BRD) on feedlot cattle production is widely cited in the veterinary literature, there is less recognition paid towards the hidden costs tied to respiratory disease in younger beef calves, as well as in dairy calves and replacement heifers. This review seeks to explore the production losses incurred in both the beef and dairy industries when respiratory disease affects calf health.

IMPACT OF RESPIRATORY DISEASE IN THE BEEF INDUSTRY
Morbidity rates due to respiratory disease in feedlot cattle have ranged widely from as low as < 10% up to 60% or greater. Mortality rates attributable to BRD generally range from 0.3–3.6% annually, and BRD is the leading cause of death in feedlot studies based on cases necropsied. High-risk weanling cattle entering the feedlot typically experience the most significant mortality and morbidity due to respiratory disease.

Annual morbidity losses due to respiratory disease in feedlot cattle have been estimated at $800 million in the beef and dairy industries of the United States (Weekley et al. 1998), and total expenditures of up to $3 billion have been experienced annually through both prophylactic and therapeutic management of BRD (Griffin 1997). Feedlot cattle treated for respiratory disease also experience reduced average daily gains compared to those seen for untreated animals, with this reduction being most evident in the first 3 months post-arrival at the feedlot (Martin et al. 1989; Bateman et al. 1990; Morck et al. 1993; Wittum et al. 1994; Galyean et al. 1995; Wittum & Perino 1995; Fulton et al. 2002; Schunicht et al. 2003; Thompson et al. 2006; Babcock et al. 2009). Reduced daily gains have been attributed to the systemic effects of inflammation on appetite and behavior, as well as the caloric costs of inflammatory protein production. Decreased gains may also be associated with different feeding practices in hospital pens during treatment for BRD, namely feeding roughage in the hospital pen (Gifford et al. 2012).

Beyond reduction in daily gain, BRD results in economic loss through poorer carcass quality in affected cattle. Gardner et al. (1999) documented decreased average daily gain and fewer Choice or Select grades for cattle treated specifically for respiratory disease during the finishing period. The reduction in carcass quality is even more dramatic for animals requiring treatment more than once during the feedlot period (Bateman et al. 1990; Morck et al. 1993; Cernicchiaro et al. 2013). A decrease in carcass value of $23.23, $30.15, and $54.01 was reported for feedlot cattle treated once, twice, or ≥ 3 times, respectively, when compared with the carcass value for non-treated cattle (Schneider et al. 2009).

Other losses include labour to treat sick animals, transport of sick animals, and carcass disposal (Salman et al. 1991; Jim, 2009). Less tangible costs associated with BRD mortality include purchase cost of the animal, cost of feed consumed during the feedlot period prior to death, and interest on invested money (Loneragan et al. 2001). BRD may also increase the cost of production by decreasing feedlot efficiency during outbreaks, through crowding of hospital facilities, suboptimal use of pen space, additional labor requirements to treat sick animals, delays in introduction of higher energy rations, as well as less time available for feedlot personnel to monitor the rest of the herd for early detection of new cases of BRD (Johnson 1985; Jim 2009). Reduced conception rates in replacement beef heifers
treated for BRD has also been documented for stocker cattle raised extensively grazing rangeland (Pinchak et al. 2004).

In consideration of the many ways in which respiratory disease impacts beef production, estimates of economic losses have been reported by many authors to consider these less tangible sources of financial drain to the industry. Griffin (1997) used an economic model to predict the impact of BRD on the costs from weaning to slaughter in feedlots. The author was able to demonstrate a 7.9% increase in production costs for BRD affected cattle when compared to cattle with no lung lesions detected at the time of slaughter. Similarly, Snowder and colleagues (2006) estimated a loss of $13.90 per animal related to BRD during the feedlot period, when losses due to reduced daily growth, treatment costs, and mortality were considered. Babcock and colleagues (2009) determined impact of BRD on feedlot performance through assessment of ADG, days on feed, hot carcass weight (HCW), quality grade and yield grade in consideration of time from arrival to first treatment or time from first treatment to slaughter. The economic impact of BRD on feedlot performance was noted to be complex, with the impact on various parameters differing depending on entry body weight of the cattle and hence days on feed. A recent multivariable assessment of the economic consequences of BRD considered the effect of one or more treatments for BRD on performance taking into account demographic variables that could also influence net profit values (Cernichiaro et al. 2013). Average daily gain, HCW, and calculated yield grade decreased with increasing number of BRD treatments. As such, net returns decreased with increasing number of treatments for BRD over the feedlot period, although the magnitude of this association was influenced by a seasonal effect; for fall arrivals, mean net return for cattle that were never treated was $39.41, whereas net returns were $29.49 for cattle treated once, $16.56 for twice and $33.00 for cattle treated 3 or more times for BRD.

Current estimates on the economic impact of bovine respiratory disease in the feedlot are likely affected by poor case detection; treatment for BRD during the feeding period correlated poorly with the incidence of lung lesions diagnosed at the time of slaughter in studies by Wittum et al. (1996), Bryant et al. (1996), Thompson et al. (2006) and Gardner et al. (1999), whereas the presence of lung lesions at slaughter was negatively correlated with ADG (Wittum et al. 1996) and reduced hot carcass weights in comparison with normal cattle (Bryant et al. 1996). Timsit and colleagues (2011) have clearly demonstrated that many apparently healthy cattle also have subclinical respiratory disease based on clinically undetected episodes of fever that occur during the first weeks after entry into a feedlot; of 449 febrile episodes, only 26% were associated with clinically detectable signs of respiratory disease. The remaining 74% of episodes were not detected through routine observation of animals by feedlot personnel, but still resulted in a reduced average daily gain in these cattle over the first 40 days on feed. The current poor sensitivity to clinically detect BRD in the feedlot setting underscores that the impact of BRD to the cattle industry may be grossly understated when economic losses are estimated using only treatment records. As case detection methods improve in the future, continued efforts to understand the economic impact of BRD on beef production are therefore warranted.

**IMPACT OF RESPIRATORY DISEASE IN THE DAIRY INDUSTRY**

Raising replacement heifer calves to advance production indices within the dairy herd represents a significant proportion of the overall costs of milk production. A recent economic simulation model estimated that rearing replacement calves represents 13% of the total costs of milk production (Mohd Nor et al. 2012). In that study, the total cost to raise a calf from 2 weeks of age through until first calving was approximately €1567 (range: €1427–1715; $1918–2305 USD). Illness during the period from birth to calving therefore has the potential to significantly impact profitability of the herd, with the most frequent calfhood diseases being diarrhea and respiratory infection (USDA 2012).

Prevalence of respiratory disease in the dairy industry has been captured through the National Animal Health Monitoring System of the USDA. A recent survey of US operations that specialize in
raising dairy heifers reported that respiratory disease is the leading cause of mortality in both preweaned (2.3%) and weaned (1.3%) heifer calves (USDA 2012). It is also an important cause of morbidity in dairy heifer calves, with 18.5% of dairy calf illness being attributable to BRD prior to weaning and an additional 11.2% of weaned calf morbidity attributed to BRD.

Like the beef industry, direct costs of BRD in preweaned and weaned dairy calves include labour and laboratory costs for detection and diagnosis, as well as veterinary fees, costs of treatments and animal mortality. The occurrence of respiratory disease in calves in the first three months of life is associated with a 2.5 times higher risk of mortality after 90 days of age (Waltner-Toews et al. 1986), reduced likelihood of entering the milking herd (Warnick et al. 1995) and higher mortality prior to calving (Warnick et al. 1995; Stanton et al. 2012) when compared with unaffected herd mates. Historically, annual costs of treating and preventing BRD were estimated at just under $15 per calf prior to weaning, and $2 per calf after weaning (Kaneene & Hurd 1990) and the financial losses of respiratory disease from birth to time of entry into the milking herd were estimated at €18.4–57.1 (approximately $16–49 USD) per animal (van der Fels-Klerx et al. 2001). It is noteworthy that these costs are historical, and that costs would be higher today and would also differ due to changes in heifer management that have developed in the past two decades. For example, economic modeling suggests that the cost associated with a single occurrence of respiratory disease in a Dutch dairy herd would be closer to €95 (€128 USD) per heifer currently (Mohd Nor et al. 2012). Replacement calf mortality has dual economic impact on dairy herd profitability through loss of the animal, but also through loss of the calf’s genetic potential in advancing herd production.

Until recently, the less tangible costs of BRD on dairy production were rarely considered, but include reduced animal growth and impact on reproductive outcome measures. Respiratory disease requiring treatment early in life (first 2–3 months of age) is associated with reduced growth in weaned heifer calves (Virtala et al. 1996; Donovan et al. 1998; Stanton et al. 2012). Calf growth, as determined by regular monitoring of weight gain, can be used as a surrogate measure of calf health in assisting producers with identification of calves that are failing to thrive due to the chronic health impacts of respiratory disease (Stanton 2009). Occurrence of respiratory disease from birth to 6 months of age also significantly decreases heifer size by 13–14 months of age (Donovan et al. 1998; Stanton et al. 2012). This ultimately affects breeding age and age at first calving in such heifers. Replacement heifers treated for respiratory disease within the first three months of life calved several months later than unaffected heifers (Correa et al. 1988; Warnick et al. 1994). Similarly, mean calving age was delayed to greater than 25 months of age in BRD-treated heifers (Stanton et al. 2012). Returns on milk yield compared to rearing costs are optimized when heifers first calve between 23–24 months of age (Pirlo et al. 2000), and delayed first calving results in higher rearing costs for milk production (Mohd Nor et al. 2012). Respiratory disease in calvings has also been associated with increased calving difficulty (Warnick et al. 1994; Stanton et al. 2012).

The impact of respiratory disease on raising dairy replacement heifers predominantly affects the period from birth to date of first calving. Studies investigating residual impact of BRD on performance or longevity beyond first calving show equivocal long-term effects. In particular, heifers with a history of respiratory disease who successfully go on to deliver their first calf have similar survival and milk production in their first lactation as do heifers that did not require prior treatment for BRD (Warnick et al. 1995; Warnick et al. 1997; Stanton et al. 2012). However, severity of respiratory disease may factor into long-term survival of heifers, since heifers that were repeatedly (4+) treated for BRD between the period from birth to first calving were half as likely to survive and remain in the herd through their first lactation (Bach et al. 2011). The delayed age at first calving for heifers treated for respiratory disease was also linked with a decreased likelihood of completing the first lactation in a recent study by Bach et al. (2011).
As awareness of the hidden costs of respiratory disease become known in the dairy industry, there is a growing trend towards focus on prevention of this disease in replacement calves. From a production standpoint, recognition of respiratory disease in the preweaned and weaned calf is also the key to minimizing economic loss from this condition. This relies heavily on appropriate employee training in BRD detection, as well as adequate treatment strategies in affected calves to optimize treatment outcomes. Attention to these principles of rearing calves is fundamental to reducing the hidden costs of respiratory disease on feed efficiency and growth, delayed time to first calving, and reduced longevity in the herd.

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How Do We Know They Hurt? Assessing Acute Pain in Cats
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In many countries, pet cats outnumber dogs, yet our understanding and treatment of pain in this species has lagged behind that for dogs. Veterinarians consider surgical procedures in dogs and cats to be equally painful, but treat cats less often. One of the main reasons for undertreatment of pain results from the difficulty in recognizing and assessing pain; other reasons include a lack of species-specific data on analgesic agents, fear of side effects and the lack of products with market authorization for cats.

To treat pain we must first recognize it and quantify it in some way so we can assess the efficacy of our interventions. Pain is a complex, multidimensional, experience with both sensory (what type of pain, where is it and how intense it is) and emotional (how it feels or how it makes you feel) components. Because animals, and some subpopulations of humans are non-verbal or rather non-lingual (for example, neonates and cognitively impaired adults), the IASP added the following important caveat to its definition of pain: “The inability to communicate (verbally) in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain relieving treatment.” Because animals lack our language, they also fall into this category and assessing their pain is problematic, but can be achieved by observing behaviour and facial expressions.

Pain is subjective and no one can “feel” another person’s pain. Even after the same surgical procedure, humans do not experience the same quality and intensity of pain, so how can we determine with any degree of certainty what an animal feels? Put simply, in most humans, pain is what the patient says it is and in animals it is what we say it is; this puts an extra burden on us to “get it right.” There is a consensus that animal pain does have an emotional component, but this is difficult to measure. There is no gold standard for assessing pain in cats at this time. Several different scoring methods that include physiologic and behavioural variables have been published, but few are validated. In dogs, the most vigorously tested acute pain scoring system is the Glasgow Composite Pain Assessment Scale. Currently, similar systems are being developed for cats. Different types and sources of pain, for example abdominal versus musculoskeletal or oral pain, may result in different behaviours, so must be considered when developing scoring systems.

In cats, the correlation between easily measured physiologic (objective) variables, such as heart rate, respiratory rate, and blood pressure, has been disappointing. No study found a consistently reliable objective measure, which is not surprising since these variables can be affected by many factors other than pain. Cats suffer from “white coat” syndrome, just as humans do; for example, fear and the stress of a journey to a veterinary hospital will alter heart rate, blood pressure and respiratory rate in most cats. Plasma cortisol and β-endorphins are components of the “stress response” to anaesthesia and surgery and much effort has gone into trying to correlate these hormones with pain in laboratory and clinical trials. In cats, plasma cortisol is unreliable as a direct indicator of pain. Pressure platform gait analysis can be successfully used in cats and this may provide an objective method of assessing pain after limb procedures, at least in research settings. Mechanical nociceptive threshold testing with devices, such as palpometers, has proved a useful technique for evaluating both primary (wound) and secondary (remote areas) hyperalgesia in cats. Changes in wound sensitivity do correlate with visual analogue scoring in cats, suggesting that an assessment of wound tenderness should be incorporated into an overall assessment protocol.

All scoring systems that depend on human observers must, by definition, be subjective to some degree and leave room for error, which could be either under-, or over-assessment of the animal’s pain. Any system that is used must be valid, reliable and sensitive. Without strictly defined criteria and use of
well-trained and experienced observers, many scoring systems are highly variable; one scoring system may show an analgesic agent to be effective, yet another will show that same analgesic to be ineffective. These differences are inevitable if a system is insensitive and results in large inter-observer variability.

The most basic pain scales are simple descriptive scales (SDS). These usually have four or five descriptors to choose from; for example “no pain,” “mild,” “moderate,” “severe/very severe” pain. Although simple to use, these scales are extremely subjective and do not detect small changes in pain. Numerical rating scales (NRS) are similar to simple descriptive scales, but with numbers assigned for ease of tabulation and analyses; for example, no pain could be assigned the number 0, and very severe pain the number 5. This system implies equal difference or weighting between each category, which is unlikely to be the case. A further development of these systems is a categorized numerical rating system where certain behaviours thought to be related to pain are chosen and assigned a value.6

In an attempt to improve on these discontinuous scales, the visual analogue scale (VAS) has been widely used in veterinary medicine. This tool consists of a continuous line, anchored at either end with a description of the limits of the scale, for example no pain at one end and severe pain at the other end. The observer places a mark vertically through the horizontal line that they think correlates to the animal they are observing and this is later translated into a number by measuring the distance of that mark from zero. Holton and others11 compared the use of a simple descriptive, numerical rating and visual analogue scales for assessing pain in dogs following surgery. They showed significant observer variability, which could be as high as 36%, with all three scales.

An extension of the classic VAS system is the dynamic and interactive visual analogue scale (DIVAS). With this system, the animals are first observed, undisturbed and from a distance. The reason for this is that some animals do not display overt pain behaviours in the presence of a caregiver, but will when they think they are unobserved - this has been documented by the use of video cameras and is likely a protective mechanism against potential “predators.”6 They are then approached, handled and encouraged to move around. Finally the surgical incision (or area of trauma) and surrounding area is gently palpated and a final overall assessment of pain is made. This approach overcomes some of the deficiencies of purely observational systems; for example, a cat may remain very still and quiet because they are painful and this would go undetected without interaction with the animal. The DIVAS system has been used to assess postoperative pain in cats,12,13 and when performed by one individual unaware of treatments it detected differences between analgesics and between treated and untreated cats.12

It is now accepted that quantitative measurements of behaviour are the most reliable methods for assessing pain in animals, and that if the methodology used to develop and validate these systems is rigorous, they can be objective with minimal observer bias.5 Multidimensional systems are particularly important when self-reporting is not possible, but must incorporate components that are proven to be sensitive and specific to pain in the species being studied. Knowledge of the normal behaviour for the individual being evaluated is important, and deviations from normal behaviour suggest pain, anxiety, fear or some combination of these. Normal behaviours should be maintained postoperatively if a cat is comfortable. Grooming is a normal behaviour, but licking excessively at a wound or incision can be an indicator of pain, so the two should be differentiated. The occurrence of new behaviours, such as a previously friendly cat becoming aggressive, or a playful and friendly cat becoming reclusive, should raise our suspicion that pain may not have been adequately addressed. Currently, there is no comprehensive published “library” of validated pain behaviours in cats, but we are beginning to learn “what pain looks like” in a feline patient. Brondani and colleagues4 have developed a multidimensional composite scale for use in cats following ovariohysterectomy. This study suggests that the following are important criteria for use in assessing acute postoperative pain in cats:

- Posture
- Comfort
- Activity
- Attitude
- Mental status
  - For example, the cat is alert and interested in its surroundings and interacts with an observer versus a cat that is not interested in its surroundings, is aggressive and tries to bite or scratch the observer
- Response to palpation of the wound and surrounding areas
- Appetite
- Vocalisation
- Miscellaneous behaviours
  - Facial expression
  - Tail activity
  - Chewing and licking at the wound
  - Flexing and extending the hind limbs

These investigators also emphasize that it is necessary to record data preoperative (baseline) for comparison.

**BEHAVIOURS SUGGESTIVE OF ACUTE PAIN IN CATS**

**Figure 1** shows a normal comfortable cat, note the facial expression and body posture in comparison to the other images. Cats that adopt a hunched posture, with their head down are likely experiencing pain (Figure 2). In one study detailed behavioural ethograms were constructed for cats before and after abdominal surgery; a hunched or tucked up posture was rarely recorded in cats before surgery but occurred on a frequent basis afterwards.\(^{14}\) It has been suggested that assessment of facial expression may measure the emotional component of pain and could be a useful tool in animals.\(^{2}\) Certainly there is evidence that pain may be expressed by the face in human neonates\(^{15}\) and in mice\(^{16}\). The presence of half-closed eyes (“squinty eyes”) in cats may correlate with pain\(^{4}\) (Figure 3). A cat sitting quietly in the back of the cage after surgery may be painful; however, pain would not be recognized if the caregiver expects to see more active signs of pain such as pacing, agitation, or vocalizing. Assessing the cat before and after a procedure is very helpful - a cat that is timid or fearful may sit at the back of the cage and try to hide before surgery therefore when this behaviour also occurs after surgery it is not unexpected and is likely not an indicator of pain. However if a cat was previously inquisitive and always up at the front of the cage and interested in what is going on but then is disinterested in its surroundings and trying to hide after a procedure, this is a significant change in normal behaviour that raises one’s suspicion about this cat’s comfort level.

**Figure 1. Normal facial expression and body posture**
In general most cats dislike any restrictive dressings or bandages and may roll around, pay excessive attention to, or try to remove these. These behaviours could indicate pain or dislike of the bandage so it is important to differentiate between these two by performing a careful assessment.

The health status of the animal, extent of surgery/injuries, and anticipated duration of analgesic drugs determine the frequency and interval of evaluations. In general, evaluations should be made hourly for the first four to six hours after surgery provided the animal has recovered from anaesthesia, has stable vital signs, and is resting comfortably. Patient response to analgesic therapy, and expected duration of analgesic drug(s) administered, will help to determine frequency of evaluations. For example, if a cat is resting comfortably following the postoperative administration of buprenorphine, it may not need to be reassessed for two to four hours. Animals should be allowed to sleep following analgesic therapy. Vital signs can often be checked without unduly disturbing a sleeping animal. In general, animals are not woken up to check their pain status; however this does not mean they should not receive their scheduled analgesics. Continuous, undisturbed observations, coupled with periodic interactive observations (open the cage, palpate wound, etc.) are likely to provide more information than occasionally observing the animal through the cage door. Unfortunately, continuous observations are not practical for most clinical situations. In general, the more frequent the observations, the more likely that subtle signs of pain will be detected.

ENDNOTES
a. International Association for the Study of Pain

REFERENCES
How Do We Know They Hurt? Assessing Chronic Pain in Cats
Sheilah Robertson, BVMS (Hons), PhD, DECVAA, DACVAA, DECAWBM (WSEL), Specialist in Welfare Science, Ethics and Law, DACAW, MRCVS
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INTRODUCTION
In the past pain has often been categorized as acute or chronic based solely on duration - the latter arbitrarily being pain that lasts more than 3–6 months. However it is now accepted that this may not be a helpful classification. It has been suggested that the terms adaptive and maladaptive be adopted; adaptive infers a normal response to tissue damage and involves an inflammatory component (for example a surgical incision) and is reversible over an expected, relatively short time period. Maladaptive pain results from changes in the spinal cord and brain that result in abnormal sensory processing and is usually persistent and is of no biological use to the patient. Maladaptive pain can result from poorly treated adaptive pain, and maladaptive pain can occur quickly in some circumstances. Ideally, pain should be classified by the underlying mechanism; for example, inflammatory or neuropathic. Taken one step further, pain occurring in different diseases or conditions would be further classified by the underlying mechanisms in that particular patient. This has been referred to as the neurobiological signature of pain in a particular disease. Having this information would better guide the practitioner in the choice of treatment. For example a diagnosis of “cancer” pain is not very helpful since the cause could be mechanical compression of a nerve, inflammation from tissue necrosis, mechanical distension of an organ or neuropathic from damage to nerves by chemotherapy agents.1

Despite an overall decline in pet ownership in the United States over the past 5 years, pet cats (estimated at 74 million) continue to outnumber dogs (estimated at 70 million).^ Total veterinary visits for dogs has increased in recent years, whereas visits for cats have declined;^ this latter information combined with the knowledge that the number of older cats has increased is worrying as it is likely many cats living with long term pain such as that associated with degenerative joint disease (DJD) are going unrecognised and untreated. The reasons for undertreating pain in cats include:
- Difficulty in recognizing, assessing or “measuring” pain in cats, both by owners and veterinary professionals (i.e., a lack of validated pain scoring tools)
- Lack of species-specific data on the safety and efficacy of analgesic agents
- Fear of side effects related to treatment
- A limited number of labelled products for long term use in cats

Clearly before one can treat pain it must be recognised and quantified in some way. When it comes to long-term or chronic pain, slowing down and being less agile is often blamed on “just getting old” and not on the pain associated with conditions, such as degenerative joint disease.

CAUSES AND EXAMPLES OF CHRONIC PAIN IN CATS
- **Musculoskeletal pain**: DJD is likely the most common cause of chronic pain in cats.
- **Post amputation pain**: neuropathic in origin
- **Diabetic neuropathy**: neuropathic in origin
- **Spinal pain**: disc related, nerve root irritation/inflammation, spondylosis/spondylitis
- **Dental/oral pain**: ulcerative and proliferative gingivostomatitis, abscess, secondary facial pain
- **Ocular pain**: uveitis, glaucoma
- **Aural pain**: dermatological causes of pain, including self-trauma
- **Visceral pain**: interstitial cystitis, recurrent pancreatitis
- **Treatment-related pain**: radiation damage resulting in burns
**DIAGNOSING CHRONIC PAIN**

Usually chronic pain is associated with a change in one or more major “domains” which can be listed as:

- **Mobility:** ability to jump, lameness or stiffness
- **Activity:** changes in sleeping patterns, length of time sleeping, less time hunting, playing or interacting with other animals or people
- **Demeanour:** more withdrawn, less tolerant of attention
- **Toileting and grooming:** inappropriate urination/defecation, missing the litter tray, matted or scruffy coat or overgroomed areas
- **Changes in appetite:** commonly associated with oral pain

**DIAGNOSING DEGENERATIVE JOINT DISEASE**

The most common cause of long-term pain in cats is degenerative joint disease. In one of the first studies designed to determine the prevalence of DJD in cats, 100 radiographs of cats over 12 years of age were retrospectively reviewed and 90% of them showed radiographic evidence of the disease. In another retrospective radiological study but this time involving cats of all ages, 22% showed evidence of joint disease on radiographs and when patient records were consulted, 33% of these cats had clinical signs. Affected cats were significantly older than the control population. These authors suggested that there may be little correlation between radiographic and clinical findings or that clinical signs of DJD in cats are not easily recognized. In another study at a University referral hospital, the prevalence of radiographic signs of DJD was 33.9% and the prevalence of clinical signs was 16.5% with most affected cats being 10 years of age or older. Diagnosing DJD involves careful history taking, physical examination and radiographic evaluation.

**BEHAVIOURS SUGGESTIVE OF DJD IN CATS**

Although there is agreement that this disease is painful and impairs mobility there are currently no validated outcome measures to assess DJD associated pain in cats. This is more challenging than in dogs because of the way dogs are included in family activities compared to cats. Lascelles and colleagues are addressing this by performing item generation and design testing to create a subjective instrument to assess activity changes caused by chronic pain in cats. To do this they have looked at cats with and without DJD and recruited owners to participate in the study. They have identified differences between the two groups with regard to walking, running, chasing objects, jumping (up and down including the height of the jump), climbing and descending stairs, playing and sleeping. Other changes in behaviour may include decreased grooming, and soiling outside the litter box, withdrawing from human interaction, hiding and dislike of being stroked or brushed. Inactivity, which may result from chronic joint pain, is much more difficult to determine in cats since they naturally sleep a lot, are often solitary and don’t usually go for walks as dogs do. Activity monitors attached to cat collars have been used to monitor daily movement in cats diagnosed with DJD during treatment.

Owners are vital when assessing DJD related pain in cats as they know the cat’s history of activity, its demeanour and can assess the cat in its own environment. In many cases it is not obvious that there has been “mobility impairment” until after intervention, usually with a nonsteroidal antiinflammatory agent. After treatment owners often remark how the cat “is back to its old self,” or jumping onto or off places it has not used for a long time.

**QUALITY OF LIFE**

Most studies related to DJD in cats have focused on “mobility impairment” (presumed to be a result of pain) and have assumed this is the most important “life altering” component of the disease. It has also been assumed that improved mobility after intervention is the best outcome measure. However, we may have made too many presumptions about what is important to cats and what contributes to their
overall quality of life (QoL). In a recent study by Benito and colleagues, only 40% of items listed by owners as being important for their cats’ QoL involved mobility. Therefore it is important to assess non-active items to fully assess the impact of diseases such as DJD on QoL in cats. Non-active items in this study that owners reported as being important included sleeping, being petted and lying in the sun. This suggests that cats should be treated as an individual and that treatment should be individualized to restore the facets of life deemed important to that cat.

**How Often Should Animals Be Assessed?**

Changes related to chronic pain tend to be more insidious and subtle and are easily missed by owners. In addition chronic disease states are rarely static, and as with people there may be good days and bad days. For these reasons starting a diary for older cats can be helpful to track changes in behaviour and activity and how interventions have, or have not worked and allow comparisons to be made over time. This type of diary may also help owners track quality of life issues more objectively. This, along with six monthly check ups with a veterinarian should keep the treatment plan and goals on track.

There is little doubt that cats are under treated for pain and a key reason for this is difficulty in recognising and measuring pain in this species. With the development of validated pain scales for both acute and chronic pain in cats and the availability of more choices for treatment their welfare should improve. Although these scales are still being developed this should not prevent anyone from choosing some sort of scoring system to use. Making this part of a clinical examination raises awareness by making us look specifically for pain in our patients - sometimes when you start looking and asking questions it is surprising what you discover.

**Endnote**

A. The 2012 U.S. Pet Ownership and Demographics Sourcebook; www.avma.org

**References**

Preventing and Treating Acute Pain in Cats
Sheilah Robertson, BVMS (Hons), PhD, DECVAA, DACVAA, DECAWB (WSEL), Specialist in Welfare Science, Ethics and Law, DACAW, MRCVS
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INTRODUCTION
Cats experience acute pain related to surgical procedures and following trauma. In the first situation preventive (preemptive) analgesia can be used and in the latter prompt initiation of analgesic treatment is important.

HOW LONG SHOULD WE TREAT?
Clinically, there are two phases associated with surgery; the first is the sensory input arising directly from the surgery itself and the second is from the resultant, more prolonged inflammatory response. It is now understood that unless an effective and appropriate level of analgesia is maintained into the postoperative period to include the duration of tissue injury associated with inflammation, “re-initiation” of pain is possible.1 To prevent prolonged or persistent postoperative pain, analgesic therapy should be started prior to surgery, maintained during surgery, be robust in the immediate postoperative period and not withdrawn until the inflammatory response has subsided. Different analgesic drugs may be used during each of these phases; for example opioids and NSAIDs may be given preoperatively along with sedative agents. Opioids may be used during surgery and in the immediate postoperative period then stopped. If there are no contraindications to their use, NSAIDs are used throughout the entire “perioperative” period and are often the only drug required in the later stages of treatment. Duration of treatment will depend on the degree of surgical trauma and resultant inflammatory response. Inflammatory mediators such as IL-6 have been measured as markers of inflammation; in one study that compared laparotomy to laparoscopy in humans the correlation between inflammatory markers, degree of surgical trauma and pain was clearly demonstrated.3 The exact duration of the inflammatory response after different types of surgical procedures in cats is not well documented but is obviously longer after orthopaedic surgery than after a simple elective ovariohysterectomy performed through a small incision.

The major classes of analgesics employed for acute pain management are:
1. Opioids
2. Nonsteroidal antiinflammatory drugs (NSAIDs)
3. Local anaesthetics
4. Alpha2-agonists
5. NMDA antagonists

OPIOIDS
Opioids are the “backbone” of most acute pain management protocols and they are much more effective when given before surgery,4 or put simply, pain is easier to prevent than treat. Historically, there has been some reluctance to use opioids in cats, but they rarely become excited when clinically appropriate doses of opioids are given and it is common to see euphoria, with purring, rolling, rubbing and kneading. In contrast to other species, opioids cause marked mydriasis in cats so they should be approached slowly, while being spoken to, so they are not startled and they should be kept away from bright light. Opioids should be given by the intravenous (IV) or intramuscular (IM) route whenever possible; several studies show that the subcutaneous route is the least effective and associated with more side effects, such as nausea and vomiting.5,6
**Side Effects**
Some opioids cause nausea, vomiting and salivation; this is common after morphine and hydromorphone but not after buprenorphine, fentanyl, methadone or butorphanol. Respiratory depression is less of an issue in animals compared to humans. If undesirable side effects occur, these can be reversed by slowly giving IV naloxone to effect.

**Morphine**
Morphine is a mu-receptor agonist opioid and can be used in cats. It has been suggested that morphine is less effective in cats when compared to dogs; this may be related to their limited production of morphine metabolites,\(^7\) or because people tend to use lower doses in cats. Cats produce very little morphine-6-glucuronide [M-6-G], which may contribute significantly to morphine’s overall analgesic effect.

**Hydromorphone**
Hydromorphone is also a mu-opioid agonist and can provide excellent analgesia in cats. It can be given intramuscularly or as an IV bolus or infusion. When given by the subcutaneous route it is less effective and causes significant nausea and vomiting.\(^5\) In cats it has been linked to postanaesthetic hyperthermia,\(^8,^9\) which is unpredictable but often severe, with temperatures reaching 42°C [107°F] in some cats.

**Fentanyl**
Fentanyl is a potent, short-acting, pure mu agonist, which is most commonly used to supplement general anaesthesia where it can be given as intermittent boluses or by infusion. Transdermal fentanyl (TDF) patches have been used for acute perioperative pain. Plasma fentanyl concentrations are variable after patch placement emphasizing the need for careful evaluation of each patient for pain. This variability may be related to the size of the patch compared to the weight of the patient, skin permeability and body temperature. The danger of accidental ingestion of patches by the veterinary patient\(^10\) or by a child who has access to the patient\(^11\) should be considered if TDF patches are used.

**Methadone**
In addition to its opioid actions (mu opioid agonist), methadone acts at the NMDA receptor,\(^12\) which is involved in the development of central sensitization.

**Buprenorphine**
Buprenorphine is the most popular opioid used in small animal practice in many countries. Transmucosal absorption through oral mucous membranes (OTM) has been demonstrated in cats.\(^13\) A sustained release preparation of buprenorphine for subcutaneous administration has been evaluated in cats undergoing ovariohysterectomy. A single sustained release dose of 120 µg/kg was as effective as 20 µg/kg buprenorphine by the OTM route given every 12 hours until 60 hours after surgery.\(^14\)

**Butorphanol**
Butorphanol is a mu-antagonist, which produces analgesia through its kappa agonist activity. Agonist-antagonist opioids, such as butorphanol, exhibit a “ceiling” effect after which increasing doses do not produce any further analgesia.\(^15\) Butorphanol appears to be an effective visceral, but poor somatic analgesic. Both clinical studies and experimental investigations indicate that butorphanol is very short acting\(^15\) and would require frequent dosing to be effective.

**Tramadol**
Tramadol exerts its action through interactions with opioid, serotonin and adrenergic receptors. It is available as an injectable and oral formulation and has good oral bioavailability in cats\(^16\) and research
models demonstrate its antinociceptive effects.\textsuperscript{17} Oral tramadol is unpalatable and difficult to administer to cats.

**Epidural Opioids**

Epidural opioids can provide long-lasting analgesic benefits to the patient with few systemic effects. The rate of complications for epidurals is low, although urinary retention is reported.\textsuperscript{18} Hydrophilic drugs, such as morphine, do not readily diffuse and remain in the epidural space providing a long duration of action and minimal systemic effects. Epidural morphine does not produce motor dysfunction and is an excellent choice of technique for perianal and hindlimb surgery, including amputation.

**LOCAL ANAESTHETICS**

Local anaesthetics can provide complete analgesia with minimal side effects. Specific locoregional blocks can be used for many different surgical procedures. Another technique is to implant a “soaker” catheter into a wound to provide a method for maintaining continuous analgesia. After fibrosarcoma removal in cats the use of a wound infusion catheter\textsuperscript{19} significantly reduced the time the cat was hospitalized. Another method for delivery of local anaesthesia is a lidocaine patch. When applied to shaved skin, high concentrations of lidocaine are detected at the site of application with minimal systemic absorption.\textsuperscript{20}

**NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)**

NSAIDs are excellent analgesics for acute pain, can provide up to 24 hours of analgesia after a single dose, and are not subject to the legal regulations of opioids. There seems to be little difference in the efficacy of the NSAIDs for the treatment of acute surgical pain.\textsuperscript{21} NSAIDs should not be used in patients that are hypovolaemic, hypotensive or with compromised renal function, and never concurrently with corticosteroids.

**\textsuperscript{2}ADRENOCEPTOR AGONISTS**

When using these drugs it is important to know that the dose required to provide sedation is lower than that needed for analgesia; for example in cats dose-dependent sedation was seen with doses of dexmedetomidine between 2 and 40 \textmu g/kg (IM), but analgesia was only associated with the highest dose.\textsuperscript{22} The main concerns with the use of alpha2-agonists are their cardiovascular effects, which include a decrease in cardiac output, stroke volume and heart rate and an increase in systemic vascular resistance.\textsuperscript{23} In an effort to utilize the analgesic properties, but avoid heavy sedation and unwanted cardiovascular effects, low doses of dexmedetomidine can be given as a constant rate infusion.

**NMDA ANTAGONISTS**

Ketamine acts at the NMDA receptor and there is great interest in using ketamine to provide analgesia and to prevent central sensitization and “wind up.” Low (subanaesthetic) infusions of ketamine, given as part of a multimodal analgesic protocol in dogs undergoing major surgery, suggest that it has beneficial effects on postoperative pain;\textsuperscript{24,25} however, there are no similar reports in cats.

**MULTIMODAL ANALGESIA**

Nociception and pain involves many steps and pathways, so it seems unlikely that one analgesic agent could completely prevent or alleviate pain. Multimodal analgesia describes the combined use of drugs that have different modes of action, work at different receptors and at different places in the “pain pathway” with the assumption this will provide superior analgesia or allow lower doses of each drug to be used, thereby lessening any adverse side effects. The most commonly used combinations of drugs are opioids and NSAIDs. In cats, a combination of buprenorphine and carprofen was superior to either drug used alone.\textsuperscript{26}
**Other Techniques for Decreasing Postoperative Pain**

Less invasive surgical techniques, such as laparoscopy, thoracoscopy, natural orifice translumenal endoscopic surgery (NOTES), and laser surgery reduce the degree of surgical trauma and therefore the inflammatory response and intensity and duration of postsurgical pain.

We are now better equipped to recognise pain in cats and many of the old fears of adverse drug effects (e.g., “opioid mania”) have been dispelled. In addition, more drugs with market authorisation for cats are becoming available; therefore cats should no longer be inadequately treated for pain.

**References**


65TH ANNUAL CONVENTION PROCEEDINGS

The following papers are compiled to accompany the presentations scheduled in the continuing education sessions at the convention. The proceedings are organized by day and by stream as follows:

FRIDAY, JULY 12

Companion Animal - Respiratory Diseases
Companion Animal - Canine Theriogenology and Pediatrics
Companion Animal - Clinical Pharmacology
Companion Animal - Infection Control, Emerging Infectious Diseases, and Zoonoses
Equine - Conditions and Management of the Neonatal Foal
Equine - Update on Older Foal Diseases
Bovine - Pain Management and Clinical Pharmacology
Integrative Medicine - Acupuncture
Localization of Respiratory Disease
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The goal of the approach to the respiratory patient, as with any patient, should be to obtain a specific diagnosis by the least invasive means possible. This approach involves first verifying that the constellation of historical and clinical signs are consistent with respiratory disease or dysfunction, localizing the dysfunction to a specific region or regions within the respiratory system, and specifying the cause of dysfunction at that site. Once respiratory disease has been verified and localized, the tools used to specify the exact nature of respiratory disease often become more invasive (e.g., diagnostic respiratory sampling) and expensive (e.g., advanced imaging, endoscopy). It is therefore critical that clinicians be able to effectively verify and localize respiratory disease noninvasively in order to facilitate the development of an efficient diagnostic plan and maximize the likelihood of a successful therapeutic plan.

HISTORY AND SIGNALMENT
The diagnostic approach to the respiratory patient begins in the exam room. Knowledge of breed- and age-specific conditions will often help to streamline the localization process. The patient signalment alone may re-prioritize your differential list. Clinicians should strive to obtain a complete and detailed patient history, including knowledge of when the patient was last normal, the rate of progression of clinical signs, and patterns of clinical signs observed with the patient in its normal environment. The clinician’s ability to demonstrate clinical signs that may be unfamiliar to clients (e.g., reverse sneezing) may also help to localize the source and nature of respiratory dysfunction. Questions should be crafted to not only localize respiratory dysfunction, but also to verify that the respiratory system is the source of the dysfunction (e.g., coughing vs. retching in cats), or to confirm that clinical signs previously attributed to other organ systems are actually respiratory in origin (e.g., vomiting vs. posttussive retching in dogs).

Historical Findings Suggestive of Respiratory Disease

Sneezing
An involuntary, expiratory reflex following irritation of the nasal cavity mucosa. The sneezing reflex is a protective mechanism that can be difficult to stifle or overcome. In some cases, the reflex is so severe that the patient may throw its head down against the floor or furniture. Sneezing is primarily an acute response and will often decrease or stop completely in cases of chronic or progressive nasal cavity disease, obstruction, or irritation.

Reverse Sneezing
A voluntary or involuntary inspiratory process involving paroxysms or series of strong, abrupt inspiratory efforts (snorts). Reverse sneezing is a response to obstruction or irritation of the nasopharynx. The patient is often standing, and in some cases walking, with the neck extended, the head tilted backward, lips pulled backward, and nostrils flared. These postural efforts result in elongation of the nasopharynx and maximal widening of the nasopharyngeal meatus. Paroxysms may last anywhere from a few seconds to a few minutes. These events frequently occur at night or while the patient is at rest, due to the passive narrowing of the nasopharynx. Although these paroxysms are not typically associated with respiratory distress, they can be quite alarming to unfamiliar or unprepared clients.

Nasal Discharge
Nasal discharge is the result of an increase in fluid secretions in the nasal cavity, a change in the quality or viscoelastic properties of nasal secretions, an impairment of nasal mucociliary clearance, or a
combination of several or all of these conditions. When visible, nasal discharge should be characterized by its appearance and consistency (mucoid, serous, hemorrhagic, etc.), as this will help to localize the source of the discharge, or to identify the mechanical reason for the discharge. It is important to note that nasal discharge may not always be obvious. Cats, as well as some dogs, can be fastidious groomers and may remove overt nasal discharge before owners are aware of its presence. In these cases, the nasal planum may become ulcerated or hyperkeratotic, and the haired skin surrounding the nasal planum may become alopecic as a result of the repeated trauma from licking or pawing at the nose to clear the discharge. Also, it is important to remember that normal mucociliary clearance in the nasal airways moves secretions from the nasal cavity caudally toward the nasopharyngeal meatus. As a result, nasal discharge may initially be directed toward the larynx, resulting in an upper airway cough (see below). Overt nasal discharge from the nostrils will not become apparent until the amount or character of the secretions exceeds the nasal mucociliary clearance capacity, or until the mucociliary clearance apparatus has been sufficiently damaged or impaired (e.g., *Bordetella*, *Mycoplasma* infections, epithelial metaplasia). Nasal discharge may also be a manifestation of non-respiratory disease (e.g., esophagopharyngeal reflux).

**Audible Respiratory Sounds**

Respiratory noises that are audible to clients without the aid of a stethoscope are almost always due to airway obstruction and are usually of upper airway origin (nasal cavity, nasopharynx, oral cavity, larynx, extrathoracic trachea). Since stress and sympathetic tone associated with the hospital visit may facilitate airway opening, it is not uncommon for respiratory noises that are present at home to be absent in the exam room. Owners should be asked to describe whether noises are continuous (stridor) or discontinuous (stertor), constant (fixed obstructions) or intermittent (dynamic or episodic obstructions), and if intermittent, what events precipitate the noise (exercise, sleep, etc.). Having owners provide video recordings of respiratory noises can be very helpful both in characterizing the sound and evaluating the patient’s posture during the event. While the determination of the phase of respiration during which the noise occurs is extremely valuable information, it can be very difficult for clients to reliably make this type of assessment.

**Cough**

Cough is a defense mechanism that protects the lower airways. It can be triggered by inhalation of noxious substances or irritants, or by the accumulation of retained substances in the large and small airways. The sound of a cough originates from the larynx as a result of the acute expulsion of intrapulmonary air through a closed glottis. However, cough may be triggered by irritation or stimulation of any portion of the tracheobronchial tree, or by laryngeal irritation. Dogs and cats with irritation or stimulation originating from different regions of the tracheobronchial tree may exhibit subtle differences in the quality of their coughing, and these differences can be very helpful in localizing the site and nature of the stimulus.

Cough originating in the alveoli or small airways (bronchopneumonia, chronic bronchitis) is usually preceded by a deep inspiration. Paroxysms may start quietly and grow louder as tracheobronchial secretions are moved up to the central airways (crescendo). These coughs may be productive or nonproductive and are frequently followed by a posttussive retch or swallowing of raised secretions.

Cough originating in the central airways (trachea, mainstem bronchi) is often associated with a “goose honk” sound, as air is forcefully expelled through segments of narrowed or collapsed airways. Paroxysms of tracheal coughing are often “non-progressive,” in which each cough sounds like the preceding one, triggers the subsequent one, and, as a result, may be quite prolonged.

Cough may also be elicited with stimulation of the larynx by postnasal drainage of nasal secretions or oral cavity contents. With laryngeal origin coughing, the stimulus is often abrupt and unanticipated, resulting in reflex laryngospasm and thus preventing deep inspiration prior to the start of the cough.
This cough is typically more of a rapid-fire cough that may be weak or ineffective due to the small volume of air expelled. This cough may also be followed by voluntary efforts to clear the upper airways (gagging).

Cough can also be induced by airway narrowing during expiration, as a result of pleural space disease (primarily dogs), cardiomegaly (dogs), or intrinsic airway narrowing secondary to dynamic small airway disease (chronic bronchitis [dogs and cats], asthma [cats]), tracheal collapse (primarily dogs), or restrictive lung diseases. This latter type of cough is typically triggered at higher tidal flows and may only be noticed during exercise in early stages of disease, but may become more noticeable as cardiopulmonary reserves are diminished. This may also be a voluntary or learned behavior, as a means of increasing airway pressure to maintain patency in collapsing airways (a form of “auto-PEEP”).

**Physical Examination of the Respiratory Patient**

The physical examination is the next step in both verifying and localizing respiratory disease. Respiratory signs may be due entirely or in part to intrinsic respiratory disease, or they may represent respiratory manifestations of dysfunction in other organ systems (e.g., gastrointestinal, CNS, cardiovascular, adrenal, thyroid). In addition, the stress associated with a nonrespiratory illness may unmask occult respiratory disease. For these reasons, it is always important to perform a complete physical exam whenever possible.

**Observation**

My examination of the respiratory patient begins with detailed observation of the patient at rest whenever possible. I try to ignore the pet and minimize my presence in the room for the first several minutes. I typically sit on the floor and quietly obtain a history from the owner. I’ll usually encourage owners of feline patients to remove them from their carriers and allow them to wander around the exam room. After a few minutes, I’ll obtain a respiratory rate, listen for respiratory noises, and assess their breathing pattern and posture. For the patient presenting in respiratory distress, I’ll still try to get a quick assessment of respiratory pattern and posture prior to handling the patient.

**Breathing Pattern**

During normal respiration, the chest wall and abdominal wall move out together during inspiration and move in together during expiration. This coordinated movement allows maximal expansion of the lungs with minimal effort during inspiration, with passive relaxation of the muscles of respiration and elastic recoil of the lungs to provide expiration. Normal ratios of inspiratory time: expiratory time are from ~1:1 to 1:1.5. Some animals at rest may exhibit a pronounced pause at the end of expiration, during which no chest or abdominal wall movements are detectable.

An increase in respiratory workload may result in an alteration in the patient’s breathing pattern. These alterations are usually strategies to minimize the work of breathing, and they will vary as a result of the nature of the increased respiratory burden.

Airway obstruction results in an increase in airway resistance, or an increase in the pressure necessary to generate airflow. The increase in respiratory effort can facilitate airway collapse and exacerbate airflow obstruction. Extrathoracic obstructions (laryngeal tumors, laryngeal paralysis, nasal or nasopharyngeal obstruction) are associated with inspiratory difficulty, while intrathoracic obstructions (small airway disease, mucus plugging, intrathoracic tracheal collapse) are associated with expiratory difficulty. A common compensatory strategy for patients experiencing airway obstruction is to decrease the velocity of airflow, thus minimizing the propensity of the airways to collapse. This results in slow, deep respirations, often with prolongation of the inspiratory phase in the case of extrathoracic (upper airway) obstructions, and expiratory phase prolongation with intrathoracic obstructions.

Restrictive lung disease results in a decrease in lung compliance or the change in lung volume associated with a measured increase in airway pressure. Patients with conditions associated with
restrictive breathing patterns (bronchopneumonia, pulmonary fibrosis, pleural space disease) will require higher airway pressures to fully expand their lungs. Because the increase in workload is associated with lung expansion, patients with restrictive lung diseases or pleural space disease may compensate by decreasing tidal volumes and increasing respiratory rates, resulting in rapid, shallow breathing.

Obstructive and restrictive conditions each increase the work of breathing. With time, an increase in the work of breathing can result in respiratory muscle fatigue, resulting in a paradoxical breathing pattern. As respiratory muscles fail, the negative intrathoracic pressure generated during inspiration will tend to suck the chest wall in. In addition, diaphragmatic fatigue can lead to recruitment of the abdominal muscles, causing outward movement of the abdominal wall during expiration. These chest and abdominal wall movements oppose those seen with normal respiration and can be indicative of severe or longstanding respiratory dysfunction.

Breathing Posture
Patients experiencing significant respiratory compromise may adopt a posture that helps maximize the efficiency of breathing. These adaptations help to decrease airway resistance by increasing airway cross-sectional area and facilitating chest wall expansion. Extending the head and neck reduces redundancy and obstruction in the pharynx. Flaring the nostrils opens the nasal valve (ostium internum). Breathing through an open mouth bypasses nasal and nasopharyngeal resistance altogether. This often represents significant loss of cardiopulmonary reserves in cats, who often maintain nasal breathing even in the face of severe airway obstruction. Patients may adopt a seated posture or prefer to remain sternal, with the elbows abducted. Patients may also minimize extraneous activity and eliminate actions that exacerbate airway narrowing (swallowing, vocalizing).

Respiratory System Examination
In many cases, the physical examination of the respiratory system serves to confirm what our history and observation suggest. However, in other cases, historical signs may be vague, and overt signs of respiratory dysfunction may be subtle or absent. A thorough examination of the respiratory system includes a nasal exam (muzzle, head, eyes, dental arcade, hard palate, nasal airflow), oral exam, cervical exam including palpation of the larynx and trachea, and thorough thoracic auscultation, including auscultation over the thoracic inlet.

Physical exam findings referable to the upper airway include stridor, stridor, and decreased or absent nasal airflow. Stertor is a discontinuous, low-pitched fluttering sound that usually originates from the nasopharyngeal meatus. It is typically associated with inspiratory dysfunction, but may also be present during both phases of respiration. Because of the tendency of the nasopharyngeal meatus to narrow during rest, stertor may be more pronounced at night. Stridor is a continuous, high-pitched inspiratory sound, usually produced as a result of narrowing of the larynx or extrathoracic trachea. In contrast to stertor, stridorous respiratory noise may be absent at rest but exacerbated by high airway flows (exercise, panting, etc.). Nasal airway patency can be assessed by placing a refrigerated glass slide in front of the nose during nasal breathing, and watching for the appearance of condensation from each nostril.

Physical exam findings referable to the lower airways include adventitial sounds (wheezes, crackles, clicks) as well as changes in the character of normal bronchovesicular sounds. Normal inspiratory flow reaches peak velocity near the end of inspiration, while normal expiratory flow reaches peak velocity near the beginning of the expiratory phase. For this reason, thoracic auscultation of normal airflow is typically loudest at end inspiration and early expiration. Changes in the volume (increased or decreased) or pattern of bronchovesicular sounds can be an early indicator of respiratory disease, even in the absence of adventitial lung sounds. Wheezes are continuous, high-pitched sounds associated with intrathoracic airway narrowing and are usually associated with expiratory dysfunction.
Crackles (or rales) are discontinuous, “popping” sounds that are primarily audible during inspiration, representing an equilibration of pressures between two regions of an obstructed airway. Fine crackles are typically alveolar or bronchiolar in origin, while loud, moist crackles usually are the result of airflow through airway secretions in central airways.

The tremendous reserve capacity of the cardiopulmonary system may necessitate the use of provocative testing during a physical exam. Detection of cardiopulmonary abnormalities may be enhanced by inducing a “sigh” (close the mouth and partially obstruct the nostrils for 4–5 breaths), by triggering a cough with gentle but firm tracheal palpation, with light or moderate exercise.
**Current Therapy for Canine Chronic Bronchitis**
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**INTRODUCTION**
Chronic bronchitis (CB) is the most common chronic respiratory impairment in dogs. The condition is defined as a chronic cough occurring for two consecutive months during the preceding year that is not attributable to another cause (e.g., neoplasia, congestive heart failure). This definition is based loosely on the definition of chronic bronchitis in humans, which is characterized by a well-defined cascade of clinical and histologic changes. The early changes are typically triggered by an inciting irritant stimulus (usually cigarette smoking) and include increases in airway mucus production, impairment of mucociliary clearance, and alterations in the local immune response. The cascade of events in dogs is similar to that seen in humans, and, if left untreated, results in a cycle of chronic inflammation, chronic cough, copious mucoid airway secretions, and decreased mucociliary clearance. This session will focus on the diagnostic approach and therapeutic management of the patient with chronic bronchitis.

**EPIDEMIOLOGY**
The average age at the time of diagnosis of chronic bronchitis is eight years of age or older, and many clients will report a several-year history of intermittent cough. All breeds of dog can be affected. Higher incidence has been reported in West Highland White Terriers, Poodles, Cocker Spaniels, Pomeranians, and German Shorthair Pointers. Many dogs afflicted with CB are obese but are typically otherwise healthy.

**DIAGNOSTIC EVALUATION**
Because chronic bronchitis is a diagnosis of exclusion, it is important to complete a full diagnostic evaluation for any dog presented with a chronic cough. Common differentials for chronic cough in dogs should include congestive heart failure, heartworm disease, pneumonia, neoplasia, infectious tracheobronchitis, and tracheal collapse. Less common conditions include foreign bodies, parasitic bronchitis, and primary ciliary dyskinesia.

The initial laboratory evaluation of the chronic bronchitis dog is an important means of characterizing the overall health of the dog, and it serves as a screen for other potential aggravating or inciting conditions. Evaluation for all animals should include CBC, serum biochemical profile, urinalysis, fecal flotation, Baermann analysis, and heartworm antigen test. Additional screening tests may include serologic testing for infectious diseases (fungal, viral, Rickettsial) and echocardiography, where indicated. Arterial blood gas analysis in the early stages of disease can be normal or may reveal mild hypoxemia due to ventilation/perfusion mismatch. Severely affected dogs may become hypercapnic due to ventilatory failure.

**DIAGNOSTIC IMAGING**
Thoracic radiographs typically show bronchial or peribronchial patterns and can also reveal secondary conditions including pneumonia, bronchiectasis, and right-sided cardiac enlargement secondary to pulmonary hypertension (cor pulmonale).

**ENDOSCOPIC ASSESSMENT**
Bronchoscopic examination in cases of chronic bronchitis usually reveals nonspecific mucosal erythema with a roughened, cobblestone, or granular appearance and copious amounts of mucus. Large airways may appear relatively normal in dogs with significant small airway collapse and mucus trapping. The
airways of severely affected dogs may have a pale appearance as a result of fibrosis. Bronchoscopy is also a valuable tool for evaluation of tracheal collapse, mainstem bronchus collapse secondary to cardiomegaly, and other large airway abnormalities (e.g., bronchoesophageal fistula, foreign bodies, luminal tumors).

**Diagnostic Sampling**

Bronchopulmonary cytology is typically characterized by non-degenerate neutrophilic inflammation. A smaller yet significant population of dogs will have cytology characterized by eosinophilic inflammation. Eosinophilic airway inflammation has historically been associated with hypersensitivity reactions and has been erroneously used to make the distinction between “allergic” bronchitis and idiopathic chronic bronchitis. While eosinophils can certainly be recruited in allergic reactions, eosinophils can also be associated with neoplastic disease (e.g., lymphosarcoma), fungal infections, and systemic parasitism. Additionally, studies in humans suggest that acute exacerbations can be associated with a transient inflammatory shift from neutrophils to eosinophils.

Most dogs with chronic bronchitis do not have active infection at the time of diagnosis. However, culture and sensitivity should always be performed on airway samples in the newly diagnosed bronchitic, in acute exacerbations of previously stable disease, or with radiographic evidence of bronchiectasis. Airway samples should be cultured for general aerobic and Mycoplasma culture.

**Therapy**

CB is a slowly progressive condition for which there is no definitive cure. In the absence of intervention, the cycle of cough-induced inflammation and inflammation-induced cough will self-perpetuate. The three goals of therapeutic intervention in chronic bronchitis are: 1) do no further harm; 2) slow the progression of the histologic changes; and 3) control the clinical signs. Because the inciting cause in dogs is rarely identified, the primary treatment of CB is based on controlling airway inflammation. Therapeutic tools commonly used in the control of CB include modulators of the inflammatory cascade, bronchodilators, antitussives, antimicrobials, environmental manipulation, and weight management. Surgical intervention may be indicated in management of severe secondary changes or exacerbating conditions (e.g., tracheal collapse, bronchiectasis).

Control of airway inflammation is the single-most effective means of ameliorating the clinical signs of CB in humans. Most of the clinical signs of CB in humans and dogs (coughing, expiratory dysfunction, and mucus hypersecretion) can be primarily or secondarily attributed to airway inflammation.

Oral corticosteroids are successful as a sole therapy in resolving the clinical signs in the majority of canine CB patients, and they have historically been considered the mainstay of therapy in veterinary medicine. The short-acting oral corticosteroids (prednisone, prednisolone) should be started at antiinflammatory doses (1–2 mg/kg/day divided BID) and tapered to the lowest effective dose. The dose reductions should initially be every 1–2 weeks until physiologic doses (0.25–0.5 mg/kg/day) are attained, at which point the dose should be maintained for 2–4 weeks. In the event of a relapse during the steroid taper, the previous dose at which signs were controlled should be reinstituted, and the duration at that dose should be doubled prior to tapering.

Side effects of oral corticosteroids are many and known and can be prohibitive in some cases. These include polydipsia, polyuria, inappropriate urination, lethargy, aggression, polyphagia, weight gain, and corticosteroid withdrawal syndrome (iatrogenic hypoadrenocorticism). In cases where control is achieved but adverse effects are intolerable, combination therapy with bronchodilators or antitussives (when appropriate) may provide control at lower steroid doses.

Inhaled corticosteroids are the standard of care in humans with CB. Advantages of inhaled steroids in humans include increased drug delivery to the affected site, significant reduction in systemic absorption, and reduction in prednisone-associated adverse effects. Anecdotal use of inhaled
Corticosteroids in dogs has been associated with improvement in clinical signs and reduction in prohibitive side effects. Fluticasone propionate (Flovent, GlaxoSmithKline) at 200-, 225-, or 250-g dose can be administered to dogs using tidal breathing with an infant spacer and facemask. At a dose of 2 puffs q 12 h, a single vial lasts approximately 30 days. Limitations to the usage of inhaled corticosteroids in veterinary medicine are many and include a lack of controlled studies demonstrating efficacy, delivery, and reduced systemic absorption, drug delivery problems, patient compliance, and cost.

Other inflammation modulators that have been historically utilized in CB include antihistamines, mast cell stabilizers, antioxidants, omega-3 fatty acids, and mucolytics. With limited experimental data available and minimal anecdotal success reported, the regular use of the therapeutics cannot be fully advocated. In addition, some therapies may do more harm than good (e.g., anticholinergic effect of antihistamines).

The role of bronchoconstriction in canine CB remains unclear. Studies supporting the use of bronchodilators in CB have demonstrated improvements in objective data (pulmonary function tests) and subjective assessments (reduction in coughing, improvement in thoracic auscultation findings, owner perception of exercise tolerance). In addition, bronchodilators appear to have a steroid-sparing effect in some cases. Bronchodilators commonly used in canine CB are the methylxanthines and the beta-2 selective.

The mechanism of methylxanthine bronchodilation was initially attributed to phosphodiesterase inhibition. It is now believed that both the mechanism of activity and mechanism of adverse effects of this class of drugs are mediated by adenosine inhibition. In addition, the methylxanthines possess additional effects, including antiinflammatory effects (sPL-A2 inhibition) and stimulation of respiratory musculature (cAMP-mediated). Metabolism of the methylxanthines is variable and, when combined with limited formulations, can make dosing quite difficult, particularly in small dogs. Because of patient-to-patient variability in therapeutic and toxic dosages, administration should start at the low end of recommended doses and increase to effect. Theophylline should be administered in slow-release formulations and should start at 5–10 mg/kg PO BID. Frequency and duration can be increased to as high as 20 mg/kg BID should clinical signs warrant and adverse effects allow. Because of an increased risk of toxicity, methylxanthines should never be coadministered with enrofloxacin.

The beta-2 agonists most commonly used are terbutaline (0.625–5.0 mg/dog PO BID) and albuterol (50 g/kg PO TID). Although the beta-2 agonists are primarily selective for beta-2 receptors, some crossover to beta-1 can occur at higher doses, resulting in tachycardia, tachyarrhythmias, excitability, and tremors. Albuterol is also available as a fast-acting inhaler (Ventolin, 50 g/dose metered dose inhaler), and can be administered in the same manner as inhaled steroids. Clinical studies in veterinary medicine evaluating the efficacy and advantage of inhaled albuterol need further attention.

As mentioned earlier, most dogs do not have active airway infections at the time of diagnosis. For this reason, antimicrobial therapy is rarely indicated in cases of CB. If indicated, therapeutic decisions should be based on culture and sensitivity results whenever possible. Empirical therapy selections (while awaiting C/S) should have coverage of common airway pathogens (Staphylococcus, Streptococcus, Pasteurella, Bordetella) and may include beta-lactams, tetracyclines, and macrolides. If radiographic evidence of pneumonia or bronchiectasis is present, spectrum of activity should be expanded to cover Gram-negative aerobes and Mycoplasma.

The cough reflex in cases of CB is usually a protective and therapeutic mechanism. Coughing aids in the clearance of excess viscid secretions and can minimize aspiration of irritants and organisms in the face of an impaired mucociliary transport system (secondary ciliary dyskinesia). For these reasons, most coughs associated with chronic bronchitis should not be directly suppressed but should be alleviated by suppression of the inflammatory cascade. Some coughs may require direct suppression and include dry, hacking, paroxysmal coughs (which may also be associated with concurrent tracheal collapse), coughs associated with cough-induced syncope, and night coughing. The most effective antitussives for use in
canine CB are the narcotic cough suppressants, including hydrocodone (0.25–1.0 mg/kg PO q 6–12 h), codeine (1–2 mg/kg PO q 6–12 h), and butorphanol (0.25–1.0 mg/kg PO q 6–12 h). The most common side effect is sedation, which can be beneficial in some cases for alleviation of night coughing. Other side effects are rare at the antitussive doses and include constipation and respiratory depression.

Obesity is a major complicating factor in the management of canine CB cases. Obesity causes decreases in thoracic wall compliance and increased abdominal pressure on the diaphragm, increasing the work of breathing. Common locations for geriatric fat deposition in dogs include pericardium, mediastinum, and the cervical and thoracic subcutaneous space - all of which have the effect of decreasing ventilatory volume. Weight management alone can improve exercise tolerance and oxygenation. The most important factors in creating a successful weight management plan are client education and reasonable goals from the start. A weight-loss plan should try to target 1–3% weight loss per week, with the expectation that this rate will decrease as the dog approaches goal weight.

Environmental modifications can also help to decrease irritant, antigenic, or traumatic stimulation of the airways. Steps to decrease airborne pollutants can include elimination of cigarette smoking in the dog’s environment, elimination of aerosol and powder cleaners or deodorants, and using room or whole-house air filtration systems. Airway humidification (bathroom “spa” therapy) can help to mobilize airway secretions. Use of harnesses instead of collars can also reduce direct stimulation of the large airways.

The overall prognosis for canine CB is poor. It is important to emphasize to clients that the goal of management of CB is reduction of clinical signs and slowing the progression of this condition. It is also important to emphasize to clients that no chronic cough is benign, and that earlier intervention can prevent or delay the onset of potentially life-threatening sequelae (e.g., syncope, hypoxemia) and irreversible structural changes (e.g., bronchiectasis, fibrosis).

References
Feline Asthma: A Pathophysiologic Basis of Therapy
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INTRODUCTION
Asthma in humans was defined over 40 years ago by the American Thoracic Society as, “...a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli, resulting in airway obstruction that is reversible, either spontaneously or as a result of treatment.” It is clinically characterized by episodic or persistent cough and wheeze, expiratory dysfunction, and a generalized increase in the work of breathing. Feline asthma has been recognized in the veterinary literature for over 90 years. It is a syndrome resulting in clinical signs similar to those in human asthma. The clinical signs of cough, wheeze, and exercise intolerance are the result of decreased airflow due to mucus accumulation, airway wall thickening, and bronchoconstriction. In the early stages of disease, these signs are readily reversible with appropriate therapy. Left unmanaged, the progressive condition can lead to worsening clinical signs, permanent respiratory impairment, and a decrease in life expectancy (Woolcock 1994). This session will describe the pathophysiology of the clinical abnormalities observed in the asthmatic cat and use this as the basis for a rational, patient-based approach to therapy.

EPIDEMIOLOGY
Although cats of any age can be afflicted, most cats with asthma are young to middle-aged at the time of initial presentation, with a median age of 5 years old. A previous study estimated the prevalence of asthma among all cats is less than 1% (Corcoran 1995). Siamese and Havana Brown breeds appear to be overrepresented, with the estimated prevalence among Siamese ~ 5% (Padrid 1996). Most asthmatics are otherwise healthy cats, although some cats may also present with concurrent sneezing and/or nasal discharge. Cats may present with a history of chronic, waxing and waning cough and mild to moderate exercise intolerance. These cats may have months to years of signs prior to presentation. Alternatively, some cats may be presented in acute respiratory crisis consisting of a sudden onset of dyspnea, tachypnea, orthopnea, and open-mouth breathing. Both of these presentations likely represent parts of a continuum of progressive disease.

DIAGNOSIS
The diagnosis of feline asthma is usually made on the basis of history, the constellation of clinical signs, and thoracic radiographs. No single pathognomonic clinical sign or diagnostic test exists that can be used to reliably diagnose asthma in cats. For this reason, it is important to exclude other common causes of acute dyspnea, wheeze, or coughing. These include (but are not limited to) chronic bronchitis, feline myocardial disease, pneumonia, neoplasia, pulmonary parasitism, and idiopathic pulmonary fibrosis. Of these, feline chronic bronchitis is the major differential to be considered in otherwise healthy cats with chronic cough. Although the pathogeneses of these diseases are quite different, the distinction between chronic bronchitis and feline asthma may not be absolutely necessary in mild cases of either condition.

Hematology, biochemistry, fecal flotation, and heartworm antigen and antibody tests should be performed in the evaluation of cats with chronic cough or acute respiratory impairment. In most asthmatic cats, these results will be normal, although some cats may have peripheral eosinophilia.

Radiographic findings typically include bronchial wall thickening and hyperinflation of lung fields. Right-sided cardiomegaly due to cor pulmonale may also occur. Lobar atelectasis and lung lobe torsion, particularly of the right middle lung lobe, are also occasionally found in asthmatic cats. The finding of
normal thoracic radiographs does not rule out the possibility of asthma, particularly in cats with presentations consistent with acute airway obstruction.

Bronchopulmonary lavage samples, when available, can be extremely valuable in the diagnosis of feline asthma. Cytology and culture samples can be obtained via endotracheal wash (ETW) or bronchoalveolar lavage (BAL). Cytology typically reveals eosinophilic inflammation but may also include neutrophils, mast cells, lymphocytes, and alveolar macrophages. Increased shedding of epithelial cells and mucus secretion can also be revealed through airway lavage.

Samples should be submitted for general aerobic and Mycoplasma culture. Mycoplasma organisms have been positively cultured from up to 25% of the airways of cats with bronchopulmonary disease (Chandler 2000; Moise 1989).

Characteristic histopathologic changes in cats with bronchial asthma include smooth-muscle hypertrophy and hyperplasia, hypertrophy of mucosal and submucosal mucus secretory cells and glands, mucosal and intramural eosinophil influx, and epithelial cell hyperplasia and erosion. Collectively, these histologic changes can be reversed with appropriate therapy early in the course of the disease. As the condition progresses, however, these changes become permanent and result in airway wall remodeling.

**Pathogenesis**
Feline asthma is believed to be similar to extrinsic (aeroallergen) asthma in humans. In this model, airborne particulate matter, irritants, or allergens trigger activity in the normal resident population of cells in the airways. These “first responder” cells include epithelial cells, mast cells, antigen-presenting cells, and lymphocytes, and ultimately lead to the generation of a T-helper 2 (Th2) lymphocyte phenotype. The activation and persistence of the Th2 phenotype lead to recruitment and activation of eosinophils, mast cells, and macrophages and subsequently to the ongoing disease manifestations and characteristic histologic changes.

Eosinophils are the major effector cells in both feline and human asthma. Eosinophilic inflammation in asthma is largely the result of the persistence of the Th2 lymphocyte phenotype and lymphocyte secretion of proinflammatory cytokines, particularly interleukin-5 (IL-5). The interaction between Th2 lymphocytes and eosinophils is an important factor in the progression of asthma and is a target of many therapeutics utilized for feline asthma. Consequences of eosinophilic inflammation include bronchoconstriction, mucus secretion, sensitization of airway mechanoreceptors (elevating the cough threshold), and smooth muscle hypertrophy. Collectively, these changes result in airway hyperresponsiveness and airway wall remodeling. Other effector cell changes in asthma progression include decreased phagocytosis by alveolar macrophages and epithelial cells, and generation and persistence of airway neutrophils.

**Therapy**
The primary clinical signs in most asthmatic cats are cough, wheeze, and expiratory dysfunction. Because these signs are largely the result of airway narrowing, it is tempting to primarily treat asthmatics with bronchodilators. Successful treatment strategies must primarily address the airway inflammation, as the inflammation is responsible for both the clinical signs and the progressive histologic changes that ultimately can lead to respiratory failure. Symptomatic therapy should be a secondary goal for those signs not completely controlled with antiinflammatory therapy. No consensus exists for the treatment of all cats with asthma. Each case should be treated individually, based on severity and frequency of clinical signs.

**Corticosteroids**
Corticosteroids are now the mainstay of asthma therapy in both humans and cats. Corticosteroids down-regulate the synthesis of proinflammatory cytokines, induce apoptosis in blood and tissue eosinophils, augment the activity of macrophages for apoptotic neutrophils and eosinophils, and
increase bronchial epithelial cell phagocytic activity (Walsh 2003). To date, the most consistent, most reliable, and most effective treatment for feline asthma is high-dose, long-term oral corticosteroids. Oral prednisolone should be started at 2–4 mg/kg/day, initially divided BID. This dose should be maintained for 10–14 days, followed by a slow taper to the lowest effective dose that controls clinical signs, with the goal of reaching alternate-day physiologic dose administration. The limitations of chronic oral corticosteroid therapy are the adverse effects, which include (but are not limited to) behavioral changes, insulin resistance, pancreatitis, polyuria and polydipsia, and immune suppression with risk of infection.

Parenteral corticosteroids can be useful in both the acute emergency presentation and chronic management of asthmatic cats. Dexamethasone (0.5–1.0 mg/kg SQ/IM/IV) or dexamethasone sodium phosphate (1 mg/kg IV) should be used with bronchodilator therapy (see below) for the initial management of the emergent asthmatic. Repository steroids (Depo-Medrol, 10–20 mg/kg IM q 2–4 weeks), while not ideal for chronic antiinflammatory therapy, can be used for short-term therapy to determine the effectiveness of corticosteroid therapy, or as a means of chronic therapy in cases in which chronic oral therapy may not be feasible.

Chronic inhaled corticosteroid therapy is now the mainstay of asthma management for most humans. Inhaled corticosteroid preparations exist as steroids alone or are combined with long-acting bronchodilators. To overcome compliance problems associated with inhalation therapy in children, spacer devices can be utilized, allowing the drug to be delivered with tidal breathing. These spacers can also be used in cats and dogs for management of chronic airway disease. Fluticasone propionate (Flovent, 220-g metered dose inhaler) can be used once a cat has been stabilized with oral or parenteral steroids. Dosing should start at 2 puffs twice daily, followed by a gradual reduction in the oral or parenteral steroids. The goal of inhaled steroid therapy should be to provide a prednisone-sparing effect; however, some cats can be completely controlled with inhalation therapy.

**Bronchodilators**

Bronchodilators should not be necessary as chronic therapy for most asthmatic cats. However, for cats in which corticosteroid therapy is not adequate to control clinical signs, bronchodilators can be used symptomatically. A more important use for bronchodilators is as early at-home intervention for asthmatic crisis. Beta-2 agonists are the most effective bronchodilators in cats. Terbutaline (0.01 mg/kg IM or SQ) can be sent home with owners, with explicit instructions for indications. Owners can be trained to administer injections in a manner similar to insulin injections. Bronchodilators can also be administered as inhalation therapy. Albuterol (90 g MDI, 2 puffs) can be used with the same spacer as that used for chronic steroid therapy. Beta-2 agonists, both inhaled and subcutaneous, are relatively short-acting (2–4 hours) and can have significant cardiac and systemic adverse effects. Beta-2 agonists should not be used in cats with hypertrophic myocardial disease, so proper screening for heart disease should precede dispensing of this medication. Combinations of inhaled corticosteroids and long-acting bronchodilators have been shown to be more effective in blocking airway inflammation and reversing bronchoconstriction in an experimental model of feline asthma (Leemans et al. 2012). I regularly use an inhaled combination of fluticasone propionate and salmeterol for cats that are steroid-responsive, but at risk of side effects at higher doses of inhaled or oral steroids.

**Antimicrobials**

Airway infection does not appear to play a major role in the pathogenesis of feline asthma. Dye et al. (1996) found significant (> 103 cfu/ml) positive BAL cultures in only 1 of 25 asthmatic cats (Bordetella bronchiseptica). Mycoplasma organisms may be an exception. As mentioned earlier, Mycoplasma spp. have been isolated from up to 25% of cats with bronchopulmonary disease. These organisms are well adapted to serve as primary lower airway pathogens. In addition, Mycoplasma spp. have been implicated as possible triggers of acute exacerbations of asthma in humans. Use of antimicrobials should
be based on culture and sensitivity whenever possible. Respiratory infection should also be considered in asthmatic cats that are not responding to corticosteroid therapy.

**Further Study**

Human asthmatic airways are exquisitely sensitive to the effects of histamine. Antihistamines can be effective in blocking acute signs in human extrinsic asthmatics prior to an expected provocation (e.g., pollen season). Feline airways, however, are not hyperresponsive to histamine challenge (Dye 1996), and this finding suggests that antihistamines may not be effective in the management of feline asthma. Feline smooth muscle does demonstrate hyperresponsiveness to serotonin challenge (Padrid 1995), and serotonin is a secretory product of feline mast cells. Cyproheptadine is an antihistamine with anti-serotonergic properties and has been demonstrated to block the smooth-muscle effects of serotonin in vitro. In addition, there have been anecdotal reports of clinical benefit associated with the use of cyproheptadine (2–4 mg PO BID; Padrid 2000) in feline asthmatics. Potential adverse effects of cyproheptadine can include sedation and polyphagia, and the anticholinergic effect of cyproheptadine can also contribute to airway drying and mucus thickening. Cyproheptadine may provide benefit in asthmatics as an additive therapy. Further study is needed before this can be advocated as a therapeutic for asthmatics.

Cyclosporine inhibits the synthesis and secretion of IL-2 by T-helper cells. In so doing, it inhibits T-cell activation and blocks the development of a Th2 phenotype and the associated Th2-eosinophil interactions. Padrid et al (1996) demonstrated that cyclosporine (10 mg/kg BID) was able to inhibit the lung functional derangements and the histologic changes (airway wall remodeling) in an experimental model of feline asthma (Padrid 1996). It is currently being used in human clinical trials as a steroid-sparing agent. Cost and unpredictable absorption may limit its clinical usefulness.

Immunotherapy may offer a future option for the management of asthmatic cats. Several immunomodulatory agents have been evaluated in experimental models. Some have been effective at blocking or blunting the eosinophilic inflammatory response (Eberhardt et al. 2004; Reinero et al. 2006). The potential for severe side effects thus far has limited the clinical utility of this option.

Tyrosine kinase inhibitors are largely known for their antineoplastic effects. However, this class of drug can also modulate allergic inflammation (Lee-Fowler et al. 2012). As with immunotherapy options, the potential for side effects, including self-limiting proteinuria, has been of concern in experimental models.

**References**


Feline Chronic Nasal Disease: Diagnostic Approach to Feline Nasal Function, Dysfunction, and Pathology
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INTRODUCTION
The cat nose is a very small, yet incredibly important organ. Normal nasal function is important in maintenance of olfactory function, but it also plays a role in appetite and behavior in cats. General causes of chronic nasal symptoms include structural, mechanical, neoplastic, parasitic, infectious, and allergic disorders. The diagnostic approach to chronic nasal disease should be designed to first identify or rule out primary nasal conditions with specific therapeutic options, then to secondarily manage chronic idiopathic inflammatory nasal conditions. The purpose of this session will be to review normal nasal structure and function in cats, to use this information to highlight the potential effects of the loss of these functions, and to provide the basis for a diagnostic approach to chronic nasal disease that can largely be accomplished without referral.

OVERVIEW OF UPPER RESPIRATORY DIAGNOSTICS
History and Signalment
A complete and accurate patient history should be the first order of business in the assessment of the patient with suspected upper respiratory disease. This should include a complete signalment of the patient (age, breed, sex, reproductive status). Despite the heavy reliance clinicians place on laboratory studies and physical exam, the relative importance of the history in ultimately obtaining a diagnosis has been affirmed by several investigators (Hampton et al. 1975; Sandler 1980; Peterson et al. 1992). This process should be treated as the first diagnostic test, as its results will help prioritize your differential diagnoses and guide your subsequent diagnostic tests.

Initial questions should be succinct attempts to determine and verify the chief complaint. Subsequent questions should be crafted to yield accurate information about the pattern, nature, duration, frequency, and severity of the symptoms related to the chief complaint(s), in order to properly localize the source of the problem. Proper interpretation of the history requires a thorough understanding of the pathophysiologic basis of symptoms attributable to the respiratory system in general, as well as those specific to the upper airways. Relevant characteristics of the major upper respiratory symptoms are discussed below.

Symptoms Suggestive of Nasal Disease
Sneezing
Nociceptors of the nasal mucosa generate several reflexes in response to nasal irritation (sneezing, secretion of airway fluid, vascular activity). These reflexes act in concordance to protect the nasal airways and, ultimately, the pulmonary airways from nasal irritants. These can include foreign bodies, mass lesions, irritant gases, aeroallergens, or anything that causes nasal discharge or irritation. The sneezing reflex is a protective reflex that generates explosive expiratory airflow in an effort to dislodge and expel material from the nasal cavity or sinuses. Sneezes can be solitary or paroxysmal. In dogs, sneezing is primarily an acute response to nasal irritation, and it tends to decrease in frequency as the stimulus becomes more chronic (Doust, Sullivan 2004). For example, an acute onset of violent, often intractable sneezing can be seen initially in dogs with nasal foreign bodies. The sneezing may subside with time, often while other clinical signs (nasal discharge, airway obstruction) become more severe. In
contrast, chronic sneezing is more commonly observed in cats and is often associated with the presence of nasal discharge.

**Reverse Sneezing**
Reverse sneezing consists of a series of voluntary, loud, labored inspiratory efforts, often associated with orthopnea (extended neck, raised head, abducted elbows). Patients usually behave normally immediately prior to and following the event. Also referred to as the “aspiration” reflex, it is a normal response to mechanical irritation of the caudal nasal cavity and nasopharyngeal mucosa. The presence of reverse sneezing localizes disease to the caudal nasal cavity, nasopharynx, or paranasal sinuses.

**Nasal Discharge**
Nasal discharge may be obvious in many cases. However, the lack of overt nasal discharge does not rule out its existence. Nasal discharge may be licked from the end of the nose, resulting in focal depigmentation of the skin just ventral to the nares. Discharge may also be directed caudally into the pharynx (by the normal action of the mucociliary clearance apparatus) and ultimately swallowed. When evident, nasal discharge should be described by its character (mucoid, serous, purulent, sanguineous, hemorrhagic), frequency (constant, intermittent), volume, and whether it is unilateral or bilateral. Nasal discharge may reflect primary nasal irritation or nasal disease. However, nasal discharge may also be a manifestation of non-nasal disease (e.g., nasal irritation from chronic regurgitation).

**Cough**
Coughing is a defense mechanism that protects the lower airways from inhaled noxious substances, and it also serves to clear inhaled or retained substances from the airways (lower and upper). The latter condition is usually the result of impaired mucociliary clearance or excessive production of airway secretions. While coughing is typically associated with the presence of lower airway disease, caudally directed nasal discharge can trigger laryngeal and/or tracheal irritation, resulting in coughing. Coughing associated with upper airway disease tends to be of an abrupt, hacking nature, as the stimulus usually triggers laryngospasm without an inspiratory phase. Localizing the cause of cough requires detailed information about its nature (dry versus moist/productive; honking versus hacking), pattern (single versus paroxysmal, nocturnal, post-excitement, post-exercise), and frequency.

**Open-Mouth/Postural Breathing**
Postural changes reflect attempts to decrease airway resistance by increasing airway cross-sectional area. In dogs, open-mouthed breathing is a common response to upper airway obstruction, while in cats, open-mouthed breathing is rare and suggests that the ventilatory reserve capacity of the respiratory system is approaching exhaustion. Extending the head and neck minimizes bending in the trachea and pharynx. Flaring the nostrils and opening the mouth minimize inspiratory resistance at the inlet. Animals may also minimize extraneous (nonrespiratory) activity and eliminate actions that exacerbate airway narrowing (swallowing, vocalizing).

**Audible Abnormal Respiratory Sounds**
Airway noises generated during respiration that are perceived by owners/clients are most likely to originate from the upper airways (nasal cavity, pharynx, larynx). Discontinuous upper airway sounds (stertor, snoring) primarily originate from the nasal cavity or nasopharynx and are usually most audible during inspiration. High-pitched, continuous upper airway sounds (stridor) are usually laryngeal in origin (e.g., laryngeal paralysis) and are also most prominent during inspiration. The presence of these airway sounds suggests partial or dynamic upper airway obstruction. Upper airway sounds that are audible during both phases of respiration may be associated with fixed obstructions (e.g., nasal tumors, choanal strictures). In contrast, changes in vocalization - also laryngeal in origin - may only be detected during expiratory activities (e.g., barking).
Nonrespiratory Clinical Signs Associated with Nasal Disease

Halitosis, difficulty eating or swallowing, and gagging may occur as a result of dental disease or caudal nasal disease. Ocular discharge (epiphora, mucoid) may occur as a result of obstruction of the outlet of the nasolacrimal duct in the anterior nasal cavity. Animals exhibiting signs of nasal disease may also exhibit vestibular signs, head-shaking, and head-scratching with nasopharyngeal polyps or middle ear disease. Neurologic signs (behavioral changes, seizures, etc.) may occur in cases of aggressive nasal disease (neoplasia, Aspergillosis, Cryptococcosis) with extension of disease through the cribiform plate into the calvarium.

Physical Examination

Upper respiratory signs may be due to primary respiratory disease, but they may also be secondary to dysfunction in other systems (e.g., gastrointestinal, nervous, cardiovascular). In addition, the physical stress associated with nonrespiratory illnesses may unmask occult respiratory disease (e.g., compensated feline idiopathic chylothorax). For these reasons, a systematic assessment of all body systems is mandatory in all patients presenting with signs of upper respiratory disease.

Breathing Pattern

Careful observation of the patient during resting breathing can assist in localizing the site of respiratory dysfunction. In dogs and cats, resting, nasal breathing should have an inspiratory:expiratory time ratio (I:E) of 1:2–1:3. With upper airway obstruction (nasal, pharyngeal, or laryngeal disease), the resulting inspiratory flow restriction prolongs the time to achieve an adequate tidal volume. The result is an exaggerated inspiratory effort with a prolonged inspiratory time and increased I:E ratio (1:1–2:1), often with an increase in respiratory noise (see above).

Examination of the Upper Respiratory Tract

Examination of the nasal cavity largely entails visual inspection and palpation of the muzzle, head, eyes, and hard palate for conformation, symmetry, and defects. The external nares and rostral aspect of the nasal passages can be visually inspected for mucous membrane color and for the presence and character of any nasal discharge. Each side of the nasal cavity should be evaluated for patency and airflow. This can be accomplished by holding a glass slide in front of each nostril and observing for condensation during expiration. The hard palate and upper dental arcade should be inspected and palpated, as invasive nasal disease may extend into the oral cavity, and dental disease (e.g., tooth root abscesses) may have nasal manifestations. Careful palpation and retro propulsion of the eyes should be performed to assess symmetry, as invasive nasal tumors or destructive mycotic rhinitis may extend into the orbit.

The oral cavity should be inspected for mucous membrane color, capillary refill time. The tonsils, tongue, sublingual area, and hard palate should be examined for defects or lesions that may cause airway obstruction. Pharyngeal function can be assessed by testing for the presence of a gag reflex. Physical examination of the upper respiratory tract should also include careful palpation of the submandibular lymph nodes, an otoscopic examination, and a complete ophthalmic examination, including evaluation of the posterior segment, to investigate for signs of systemic or infectious diseases that may have nasal and ophthalmic manifestations (e.g., fungal disease, hypertension).

Diagnostic Imaging

In veterinary medicine, the investigation of suspected nasal disease relies extensively on diagnostic imaging of the upper airways (nasal cavity, pharynx, and larynx) and related nonrespiratory structures (skull, dental arcade, bony orbits, lymph nodes, salivary glands). All upper airway diagnostic imaging studies should be performed under general anesthesia. All diagnostic imaging studies should be performed prior to more invasive procedures (rhinoscopy, nasal biopsies, etc.), so that iatrogenic
hemorrhage and disruption of normal nasal structures do not affect the diagnostic utility of imaging studies.

**Nasal Radiography**
Nasal radiographs can be helpful in localization and characterization of intranasal disease. Nasal and sinus radiographs, however, rarely identify a specific cause for nasal disease (an exception would be a radiopaque foreign body). Benefits of nasal radiographs include the ability to detect asymmetry, bony destruction, and soft tissue opacity in the nasal cavity and surrounding structures. High-quality nasal radiographs can also be obtained with minimal cost and technical complexity and do not require specialized equipment. Nasal radiographs should include a minimum of two orthogonal views. Standard views include dorsoventral, open-mouth ventrodorsal (occlusal), and lateral. Specialized views (oblique lateral view, skyline view) can be extremely valuable in detecting frontal sinus and auditory bulla involvement. Dental radiographs can provide detailed information about the involvement of the maxillary dental arcade and tooth roots in the pathogenesis of nasal disease.

A disadvantage of nasal radiographs is that they lack the sensitivity and level of detail obtained with specialized techniques. The complexity of the canine and feline skull can make detection of early or subtle nasal lesions difficult. While not technically challenging, patient positioning is an extremely important factor in determining the diagnostic utility of nasal radiographs. Poor patient positioning can result in nondiagnostic images or possibly result in a misdiagnosis.

**Computed Tomography (CT)**
CT provides a detailed, three-dimensional view of the nasal cavity and sinuses. Because of the higher sensitivity and resolution of CT, it is considered the test of choice for evaluation of nasal disease. Images obtained with this modality are superior for the detection of early nasal lesions, for determining the extent of invasive nasal disease (e.g., into cribiform plate, orbital involvement). While rhinoscopy and nasal radiography are insensitive in distinguishing noninfectious rhinitis from neoplasia and/or mycotic rhinitis, the addition of CT provides valuable detail of characteristics that can be strongly suggestive of one of the more aggressive processes. CT is particularly sensitive in detecting changes in bony and cartilaginous structures associated with the nasal cavity. CT alone provides no better distinction of soft tissue structures versus fluid than nasal radiographs. However, the addition of intravenous contrast causes enhancement of vascular structures in CT images that can further aid in the delineation of the margins of invasive nasal tumors, and it can be used to distinguish between fluid or mucus accumulation and soft tissue structures. Measurements and 3-D reconstructions of CT images can be used to guide subsequent nasal biopsies, and they are used in planning of surgical approaches and radiation therapy protocols.

**Magnetic Resonance Imaging**
Magnetic resonance imaging (MRI) provides resolution of soft tissue structures greater than that obtained with radiography and CT. It is superior to CT and radiography in the detection of subtle soft tissue lesions, including early neoplasms and fungal granulomas, and it can be used to readily distinguish between soft tissue structures and accumulated fluid or mucus (Doust, Sullivan 2004). MRI is currently the imaging modality of choice for investigation of nasal disease in people, and its diagnostic utility in veterinary medicine has also been well established. A limitation of MRI is that, unlike CT, it is relatively insensitive in detecting bony or cartilaginous changes. Other limitations are similar to those of CT, including cost, availability of equipment, and the requirement of technical skill and training to operate equipment and interpret results.
Specialized Diagnostic Procedures - Direct Visualization and Sampling

Rhinoscopy
Rhinoscopy provides direct visualization of the nasal cavity and nasopharynx. This type of examination is indicated as part of the diagnostic evaluation of any patient presenting with signs referable to the nasal airways (see above). Rhinoscopy can provide information about the location, nature, and extent of nasal disease or airflow obstruction. Rhinoscopy, when combined with nasal cavity imaging (CT) and oral cavity examination, provides a complete evaluation of the nasal cavity. Under most circumstances, however, rhinoscopy alone is of limited diagnostic utility. Rhinoscopic appearance of the nasal mucosa is not a sensitive means of determining the cytologic or histologic nature of nasal disease. The correlation between rhinoscopic appearance and histologic assessment of rhinitis is weak, particularly in the nasal airways of cats. However, rhinoscopy significantly increases the diagnostic utility and accuracy of cytologic and histopathologic nasal samples (see below).

Due to extremely sensitive nasal airway reflexes, rhinoscopy must be performed under deep anesthesia and should only be performed after all imaging studies have been completed. The nasopharynx should be examined first, because iatrogenic hemorrhage induced by nasal cavity endoscopy can pool in the nasopharynx, possibly obscuring visualization of other nasopharyngeal abnormalities. The nasopharynx, choanae, and caudal nares can be readily evaluated via retroflex rhinopharyngoscopy. This involves maneuvering a flexible endoscope (2- to 5-mm outer diameter, 30-cm length) through the oral cavity and redirecting it dorsally over the soft palate.

The left and right nasal passages can then be examined by directing a rigid or flexible endoscope through the nares. Prior to anterior rhinoscopy, nasal flushing, and nasal biopsy, the nasopharynx should be packed closed by placing a secured stack of gauze 4 x 4 sponges tightly in the oropharynx to dorsally displace the soft palate. It is also important to check the cuff of the endotracheal tube for proper inflation. This prevents aspiration of fluid or stray tissue samples from the nasal cavity. For medium- to large-breed dogs, a flexible endoscope allows effective visualization of the anterior nasal cavity, including the dorsal meatus. In smaller dogs and cats, the small size of the naris and obstruction from the alar fold limit the utility of flexible endoscopes. Furthermore, the complex structure of the turbinates limits access to the dorsal meatus, even with smaller rigid scopes. For this reason, some nasal lesions could be missed with rhinoscopy alone, which further illustrates the importance of advanced imaging where available.

In most normal nasal airways, an endoscope directed into the ventral meatus and ventral to the turbinates should reach the choanae, allowing visualization of the nasal cavity, turbinates, and the posterior nasopharynx. Nasal airway obstruction can occur with soft tissue masses, nasal foreign bodies, and inspissated nasal secretions. Increased patency of the nasal airways, indicating turbinate loss, can be suggestive of fungal rhinitis or a destructive chronic rhinitis. Mucosal abnormalities, space-occupying lesions, and excessive airway secretions can typically be visualized in the nasopharynx or nasal passages via rhinoscopy.

Nasal Cytology
Nasal fluid or tissue samples submitted for cytological examination can be useful as a screening test for intranasal disease. Cytology can be performed on nasal biopsy samples collected for histopathological examination by gently pressing or rolling the biopsy specimen on a clean glass slide. Excess mucus and blood should be gently blotted from the surface of the tissue prior to making impressions for cytology. Guarded cytology brushes can also be used to generate samples for nasal cytology. These samples can be harvested either via blind swabs or with endoscopic guidance. Brush samples can either be rolled gently onto a slide for direct cytology or be dispersed into a small volume of buffered saline solution for centrifugation (Cytospin®) preparation.
Nasal flushing is a simple, minimally invasive procedure that can be used to harvest nasal samples suitable for cytology. While nasal flush cytologic samples should not routinely be relied upon to yield a definitive diagnosis, cytology of nasal flush samples has been shown to correlate with histopathologic diagnoses in approximately 50% of dogs with nasal neoplasms. Nasal flush samples can be collected by placing a red rubber catheter into one nares and alternating between flushing and aspirating buffered saline into each nasal cavity to obtain fluid and tissue samples. Alternatively, fluid can be flushed into the nasal cavity and collected from the nares. The dog should be positioned in sternal recumbency with its nose hanging over the edge of the table. Using a red rubber catheter and a syringe, saline can be vigorously flushed into one side of the nasal cavity and collected as it drains through both nares. Fluid samples collected for cytology should be submitted for direct and centrifugation cytology and examined for the presence of neoplastic epithelial cells, inflammatory cells, fungal hyphae or yeast, and intracellular bacteria.

**Nasal Biopsy**

Biopsy specimens from the nasal cavity can be obtained through a variety of blind or guided methods. With any type of biopsy method, care must be taken to avoid penetrating the cribiform plate during sample harvesting. The medial canthus of the eye is considered a conservative guide for the caudal extent to which blind biopsies can be safely obtained. Because of the risk of significant hemorrhage, coagulation status (PT and aPTT or ACT), platelet function (BMBT), and blood pressure should be assessed prior to obtaining nasal biopsies. Coagulopathy, severe thrombocytopenia, platelet dysfunction, and hypertension are all contraindications to nasal biopsy. Biopsy samples can be processed for histopathology, macerated tissue culture for general bacteriology and mycology, and impression smears for cytology.

Blind biopsy collection techniques include cup (arthroscopic) or pinch biopsy forceps, straight hemostatic forceps (cats), or aspiration techniques, using a rigid plastic tube (polypropylene or polyethylene, 5-mm diameter), advanced to the level of the lesion (as determined by prior imaging studies) under gentle suction. Rhinoscopy can also be used to guide nasal biopsies. Pinch or cup biopsy forceps can be passed through or beside the endoscope to obtain deep mucosal sections of identified nasal lesions.

Saline hydropulsion is a novel, relatively noninvasive technique that allows for collection of samples from nasal masses without the need for biopsy equipment. Saline hydropulsion is performed in dogs using a 20- to 60-cc catheter-tip syringe containing room-temperature saline. In small dogs and cats, a Luer-tip syringe should be used. With the nasopharynx securely packed off with gauze (see above), the catheter tip is wedged into one nostril, and the saline is forcefully infused (hydropulsed) into the nasal cavity. The process is repeated in the contralateral nares. Tissue fragments can be collected from the fluid draining out of the nostrils, or they can be collected from the gauze in the oropharynx and preserved in an appropriate fixation solution for histopathological evaluation. In addition to providing tissue samples for histopathologic and microbiological analysis, this technique can provide some clinical relief by debulking tumor mass and alleviating airway obstruction.

Sampling of lesions in the nasopharynx and caudal nasal cavity can present a diagnostic challenge. Biopsy of nasopharyngeal lesion can be accomplished endoscopically via retroflex rhinopharyngoscopy. The biopsy instrument should be pre-placed through the biopsy channel prior to 180° flexion (never pass an instrument through a fully flexed endoscope), then retroflexed over the soft palate to visualize and biopsy the nasopharyngeal lesion. Alternatively, a flexible endoscope can be retroflexed into the nasopharynx and used to visualize the nasopharyngeal lesion while biopsy forceps are passed anterograde through the nares. In some circumstances, a spay hook can be used to retract the soft palate from the oral cavity, and biopsy forceps can be passed through the mouth to blindly biopsy the nasopharyngeal mucosa.
Hemorrhage is the major complication of nasal biopsy. Most bleeding can be managed by flushing the nasal cavity with cold saline following the biopsy procedure. With persistent bleeding, racemic epinephrine can be diluted 1:100,000 in cold saline and flushed into the nasal cavity. In cats, ophthalmic preparations of phenylephrine (2.5%) can be dropped directly into the nasal cavity, or cotton-tipped applicators can be soaked in a mixture of 5% lidocaine with 0.5% phenylephrine and packed into the nostrils for 5–10 minutes.

**Nasal Culture**
The normal nasal airways are colonized with a population of mixed bacteria and fungi, which can confound results obtained from routine culture of nasal secretions and nasal swabs. Primary bacterial rhinitis is extremely rare in the dog and cat, and bacterial infections of the nasal cavity are always considered secondary to another disease process that disrupts the mucosal barrier and innate immune function (e.g., fungal rhinitis, neoplasia, viral infection, foreign bodies, trauma). Bacterial culture is considered significant if there is heavy growth of a single organism. Macerated tissue culture of nasal biopsies is of higher diagnostic value than culture of nasal secretions or nasal flush specimens. Positive fungal cultures in symptomatic dogs should be considered accurate.

**Dorsal Rhinotomy**
Diagnostic dorsal rhinotomy is rarely performed but remains a viable option when other attempts at diagnosis have failed. Dorsal rhinotomy has the advantage of being therapeutic as well, particularly in cases of debulking nasal neoplasms, and providing an opportunity for direct application of topical antifungal medications for mycotic rhinitis. As with nasal biopsies, the major complication of dorsal rhinotomy is hemorrhage, which can be of a severity to necessitate fluid resuscitation or transfusion (Doust, Sullivan 2004).

**REFERENCES**
**Feline Chronic Nasal Disease: A Structural and Functional Approach to Therapy**
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**INTRODUCTION**
Chronic nasal disease is a common problem in cats, an important cause of significant morbidity in feline patients, and a source of frustration for veterinarians, our clients and our patients. Symptoms of nasal disease may be caused by any of a myriad of primary respiratory disorders or nonrespiratory causes. Idiopathic chronic rhinitis is one of the most common chronic nasal disorders in cats. It is a diagnosis made by exclusion of other disorders, and usually requires chronic management. Other causes of chronic nasal disease include structural, mechanical, neoplastic, parasitic, infectious, and allergic disorders. The diagnostic approach to chronic nasal disease should be designed to first identify or rule out primary nasal conditions with specific therapeutic options, then to secondarily manage chronic idiopathic inflammatory nasal conditions. Treatment of secondary infections and symptomatic therapy should be tertiary goals. The purpose of this session will be to review normal nasal structure and function in cats, to review the diagnostic approach to chronic nasal disease, and to discuss a therapeutic approach to chronic nasal disease based on feline nasal structure and function, with a focus on diagnostic and management options for idiopathic chronic rhinitis that can be done without referral.

**OVERVIEW OF FELINE NASAL STRUCTURE AND FUNCTION**
The nose is a structurally and functionally complex organ in the upper respiratory tract. It is the primary site of entry for inhaled air in the feline respiratory system and therefore has many important and diverse functions. The nasal cavity functions to efficiently filter, warm, and humidify inhaled air before it enters the more delicate distal tracheobronchial airways and alveolar parenchyma of the lung. The nose serves as the principal organ for olfaction (the sense of smell). In addition to olfactory sensory function, the nasal cavity also serves as a sensory organ for the detection of irritants and noxious inhaled substances.

**Gross and Functional Anatomy of the Nose**
The feline nasal airway is divided into two passages by the nasal septum. Each nasal passage extends from the nostrils to the nasopharynx. The nasopharynx is defined as the airway posterior to the termination of the nasal septum and proximal to the termination of the soft palate. Inhaled air flows through the nostril openings, or nares, into the vestibule, which is a slight dilatation just inside the nares and before the main chamber of the nose. Unlike the more distal main nasal chamber that is surrounded by bone, the nasal vestibule is surrounded primarily by more flexible cartilage. The luminal surface is lined by a squamous epithelium similar to that of external skin.

The rostral main chamber in cats has two turbinates, the maxilloturbinate and the nasoturbinate, which emanate medially from the lateral wall of the main chamber. The main chamber is divided by the maxilloturbinate and nasoturbinate into a dorsal, middle, and ventral meatus. These turbinates are lined by mucosa containing abundant capacitance vessels that are under autonomic control. Dilation of these vessels causes engorgement of the erectile mucosal tissue, leading to nasal congestion. In the caudal main chamber, the ethmoturbinates emanate rostrally from the dorsal septum and the ethmoid bone. These turbinates are primarily lined by olfactory epithelium and contribute to the acute olfactory capacity of cats. Feline turbinates have complex folding and branching patterns that serve to increase nasal airway surface area for filtration, absorption, conditioning, and clearance. These turbinates also divide the nasal airspace into multiple narrow, tortuous columns that are vulnerable to obstruction.
**Nasal Breathing**
The upper airways provide the majority of the resistance in the respiratory tree (up to 75% of the inspiratory resistance). While cats are technically capable oronasal breathers, many cats will maintain nasal breathing, even in the face of severe nasal obstruction or cardiopulmonary dysfunction. A switch to oral breathing in a cat usually suggests that there is a significant reduction in cardiopulmonary reserve. It is therefore very important that nasal airway patency be preserved in cats presenting with any type of respiratory dysfunction.

After passing through the nasal vestibule, inhaled air courses through the narrowest part of the entire respiratory tract, the nasal valve (ostium internum), into the main nasal chamber. All nasally inspired air passes through the main chamber into the nasopharyngeal meatus prior to passage through the laryngopharynx into the lower airways. The cross-sectional area of the nasal airways decreases by 4–5x between the main chamber and the nasopharynx, requiring an increase in flow rate to accommodate bulk flow. Because of this abrupt change in airway caliber at this site, even minor changes in the diameter of the nasopharyngeal airway lumen can have profound effects on inspiratory airflow and respiratory effort.

**Nasal Filtration and Mucociliary Clearance**
Most of the luminal surfaces of the nasal mucosa (with the exception of the most proximal regions of the nasal vestibule) are covered by mucus. Its physical and chemical properties are well suited for its role as an upper airway defense mechanism, filtering the inhaled air by trapping inhaled particles and certain gases or vapors. The mucus is produced by mucous (goblet) cells in the surface respiratory epithelium and subepithelial glands in the lamina propria. The synchronized beating of surface cilia propels the mucus and entrapped particulates from the main nasal chamber caudally to the nasopharyngeal meatus. With normal nasal function, secretions pass through a ring of nasal-associated lymphoid tissue (NALT) surrounding the caudal aspect of the nasopharynx. Since this site is one of the first lines of defense against inhaled pathogens, dusts, and irritant gases, compromises in mucociliary clearance could lead to increased nasal infections and increased susceptibility to lower respiratory tract diseases. From this site, nasopharyngeal contents are cleared to the oropharynx, where they can be swallowed into the esophagus and cleared through the digestive tract or expectorated.

**Olfactory Function**
The ethmoturbinates lining the dorsal and caudal main chamber of the nasal cavity are lined by olfactory epithelium, a sensory neuroepithelium that is responsible for olfactory function. This epithelium contains bipolar neurons that pass through the cribriform plate and synapse directly in the olfactory bulb of the brain. The vomeronasal organ (VNO), a paired tube-like structure in the ventral nasal cavity, is an important sensory organ of the accessory olfactory system. The VNO is involved in the detection and processing of pheromones and can influence behavior and appetite in cats.

**Diagnostic Approach to Nasal Diseases in Cats**
The initial approach to the patient with suspected nasal disease should be designed to verify that the patient’s clinical signs and symptoms are due to nasal disease, and to localize the problem to a specific region or regions in the respiratory tract. Once the condition has been localized as precisely as possible, specialized diagnostic procedures can be employed to obtain a diagnosis.

For many reasons (cost, time, patient stability, etc.), the typical approach to most patients involves using the least invasive diagnostic tests early, and reserving more invasive diagnostic tests for later in the diagnostic process. When possible, I recommend staging the diagnostic process to rule out differential diagnoses in a slightly different way.

Because many cases of nasal disease are eventually treated empirically or symptomatically, I try to evaluate for the conditions that I know will not respond to routine empirical therapeutic options as early
as possible. These include nonrespiratory causes of nasal symptoms (alimentary, regurgitation and reflux, tooth root abscesses, hypertension, coagulopathies) and structural obstructive abnormalities (choanal atresia, choanal strictures, nasopharyngeal polyps, nasopharyngeal stenosis, nasopharyngeal turbinates, nasal foreign bodies). Next, I try to evaluate for neoplastic differentials. These may be life-threatening or time-sensitive. Clients may be more inclined to treat nasal tumors if they’re diagnosed early in the course of disease. Next, I evaluate for differentials for which specific treatments (curative or palliative) exist. These include parasitic causes (mites, nematodes, *Cuterebra*), infectious causes (viral rhinitis, fungal rhinitis), and allergic rhinitis. My goal is to arrive at a diagnosis of idiopathic chronic rhinitis with the knowledge that nonrespiratory, anatomic, neoplastic, and potentially curable causes have been ruled out as much as possible, in order to maximize the likelihood of treatment success for a condition that is difficult and frustrating to manage.

**Minimum Database**

My diagnostic approach starts with a CBC, serum chemistry, urinalysis, coagulation profile (in rare feline cases of epistaxis), and a blood pressure. In young cats for whom viral causes of rhinosinusitis +/- conjunctivitis are likely, I collect deep conjunctival, nasal, and tonsillar swabs for detection of feline herpesvirus and feline calicivirus by PCR. These tests are highly sensitive, particularly during active outbreaks, but may not detect latent viral infection during quiescent periods. Knowledge of this diagnosis early in cats can offer important prognostic information to clients.

**Diagnostic Imaging**

The three-dimensional evaluation offered by advanced imaging modalities (CT, MRI) is extremely valuable in the assessment of space-occupying or obstructive nasal diseases. In many cases, however, useful and even diagnostic information can be obtained from a single, straight, intraoral, dorsoventral or ventrodorsal radiograph. This view allows for the assessment of symmetry or asymmetry between the left and right nasal cavities, turbinate loss, mass effect, and nasal foreign bodies.

**Rhinocopy**

Nasal endoscopy provides a detailed visual assessment of the nasal airspace and mucosal surfaces. Because of the strong nasal irritant reflex, rhinocopy should only be performed under general anesthesia. If imaging studies are planned (CT, radiographs), they should be performed prior to rhinocopy, as the presence of the endoscope causes hemorrhage, which can interfere with the interpretation of nasal imaging studies. Retroflex nasopharyngoscopy is typically performed with a flexible endoscope placed in the oropharynx and flexed 180° over the soft palate, providing a visual assessment of the walls and airspace of the nasopharyngeal meatus, and the choanae. Rigid endoscopes can also provide limited views of the nasopharynx and caudal nasal cavity by retracting the soft palate rostrally with a spay hook and directing the endoscope dorsally and rostrally into the nasopharynx. Anterior rhinocopy is best performed with a rigid arthroscopy or cystoscopy directed through the nares into the left and right nasal cavities.

In addition to providing a direct visual assessment of the nasal cavity, rhinocopy can also be used to guide diagnostic sampling of the nasal cavity (samples for cytology, histopathology), and it can also be used for therapeutic intervention (e.g., nasal flushing).

**Diagnostic Nasal Sampling**

Because of the risk of potential complications, a lack of specialized equipment, and uncertainty about indications and interpretation of results, many practitioners consider diagnostic sampling of the respiratory system to be a daunting task. However, for many causes of nasal disease, there exist no pathognomonic hematologic or radiographic findings, making cytologic or histopathologic evidence of the condition the gold standard for diagnosis. With potential risks (chronic antibiotic therapy, steroidal or nonsteroidal antiinflammatory, immunosuppressives) and potential costs (aerosol therapy)
associated with empirical and symptomatic therapy, a specific diagnosis should be sought whenever possible. There are several techniques available that will allow the safe and successful collection of samples for cytologic, histopathologic, and microbiological analysis in a general practice setting.

Diagnostic samples from the nasal cavity and nasopharyngeal meatus should always be collected from anesthetized patients. Patients should be intubated with a cuffed endotracheal tube. The oropharynx should be packed with gauze to prevent aspiration of nasal contents during sampling. Patients should be positioned with the head level or with the nose tipped slightly downward to facilitate collection of flush samples. Sampling devices should not be inserted caudal to the level of the medial canthus of the eye, to prevent possible trauma to the cribriform plate.

Cytologic samples from the airway surface can be collected using nasal flushing, cytology brushes, swabs, or impression smears from harvested tissue samples. Since collection of surface samples is safe and relatively easy, one could argue that they are indicated in the evaluation of any case of airway obstruction, nasal discharge, sneezing, or reverse sneezing. The trap in collecting cytologic samples is the risk of over-interpreting results. In general, nasal cytology is poorly correlated with histopathology, and surface samples should not be submitted for microbiological culture. However, cytologic results can be reliable for certain conditions, including fungal rhinitis, allergic inflammation, and lymphoma.1,2

Flushing can be performed in cats using a 5-Fr or 8-Fr red rubber catheter or by inserting the Luer tip of a 20-cc syringe directly into the nostril. Each lavage should be performed using 5–10 ml of room-temperature buffered saline. Lavage fluid should be collected from both nostrils. Intact pieces of tissue or debris can be gently squashed between two slides, while fluid samples can be submitted for direct and cytospin preparation. Samples collected using nasal swabs or cytology brushes can be gently rolled onto microscope slides or dispersed in EDTA (purple-top tube).

Tissue samples for histopathology and macerated tissue culture can be collected by several techniques. A coagulation profile, platelet count, and blood pressure should be obtained prior to collecting nasal biopsies. Because of the small size of the nostrils and nasal cavity, most nasal biopsies are collected blindly, but rhinoscopic and diagnostic imaging studies can be used to estimate the intranasal location of lesions. Arthroscopic biopsy forceps can be used to collect turbinate biopsies and biopsies of focal lesions. Traumatic flushing or traumatic catheterization techniques can yield tissue fragments that are of suitable size and quality for histopathology and culture. Samples are collected using a 5- to 7-Fr polypropylene catheter with the tip cut at a 45° angle. Small, staggered notches can be cut into the length of larger catheters using a scalpel blade. 5-ml aliquots of buffered saline are repeatedly flushed into and aspirated from the nose while the catheter is raked along the nasal mucosa. Saline hydropulsion3 is a less traumatic technique that can be useful for collecting samples from friable masses (e.g., necrotic tumors, fungal granulomas). A 20-cc Luer-tip syringe filled with saline is placed directly into one nostril, while the contralateral nostril is digitally occluded. Saline is forcefully pulsed into the nasal cavity to dislodge tissue fragments, which can be collected in the draining lavage fluid or cleared from the oropharynx after removal of the gauze packing.

Therapeutic Strategy for Idiopathic Chronic Rhinitis
Once structural and anatomic abnormalities have been addressed, and other treatable causes of chronic nasal disease have been ruled out, a management plan for chronic idiopathic rhinitis should be developed. When possible, nasal biopsies should be collected for histopathology and culture. Most nasal biopsies will exhibit a combination of lymphocytic, plasmacytic, and neutrophilic inflammation in the nasal mucosa, with no identified etiologic agents. After biopsy, the nasal cavity should be vigorously flushed with room-temperature saline to stop post-biopsy hemorrhage and to clear the nasal cavity of mucus and debris. This clearance of the nasal cavity helps to maximize the opportunity for a successful therapeutic plan, which should be treated in stages.
Secondary bacterial infections should first be treated, ideally with antibiotic selection based on tissue culture and sensitivity profiles. Lipid-soluble antibiotics that achieve high concentrations in airway fluid are good first choices. When antibiotic selection is not based on culture results, empirical choices should be broad spectrum, including activity against common nasal opportunistic pathogens including *Mycoplasma* spp. and *Bordetella*. Macrolides and azalides (e.g., azithromycin), fluoroquinolones, and tetracyclines are good empirical choices and should be employed for three weeks.

Once secondary infections have been treated, I determine whether or not the rhinitis is corticosteroid-responsive with a trial of antiinflammatory prednisolone. I typically start at 2 mg/kg/day for 14 days, with regular communication with the client during this time. Ideally, if cats are corticosteroid-responsive, I recommend starting a training period with a facemask and spacer device, and implementing inhaled corticosteroid therapy as soon as possible. I start at high inhaled doses of fluticasone propionate (220 µg metered dose inhaler), 2 puffs twice daily with a facemask and spacer device. Once inhalation therapy has comfortably been implemented, I start 25% dose reductions of the oral prednisolone every two weeks, with regular monitoring of clinical signs during the dose reduction. For cats who are prednisolone-responsive but may not be candidates for inhalation therapy, I recommend a longer course of therapy at 2 mg/kg/day (up to 1 month), followed by a more gradual dose reduction (25% reduction every 3–4 weeks).

For cats with lymphoplasmacytic rhinitis who are not prednisolone-responsive, or for those patients who are prednisolone-intolerant or poor candidates for corticosteroid therapy, I usually start lymphotoxic therapy with an alkylation agent. Chlorambucil is well tolerated in cats and has anecdotally been associated with improvements in clinical signs in some cases of prednisone-unresponsive chronic rhinitis. I start at 2 mg orally per cat every 48 hours. Monitoring should include a CBC prior to the start of therapy, with follow-up CBCs at 7 days, 1 month, and then every 3 months.

In cats with ongoing inflammation or severe turbinate loss, recurrent bacterial infections are an unfortunate but expected complication. These will typically manifest as an acute change in the volume and quality of nasal discharge and a new onset of sneezing in a previously controlled patient. Since it may not be practical to biopsy and culture the nasal cavity with each flare, many recurrent infections will require empirical therapy. These infections should be treated based on the frequency of their recurrence. Infrequent infections can be treated as they occur. More frequent infections may respond to prophylactic antibiotic therapy (1 week per month). As a last resort for frequently recurring infections, chronic antibiotic therapy protocols can be employed. Macrolide/azalide antibiotics can be employed chronically using every-other-day or every-third-day protocols (5–10 mg/kg every 72 hours).

Symptomatic therapy may also be an important management component of idiopathic chronic rhinitis. Most techniques are designed to facilitate nasal mucociliary clearance. Commercially available pediatric saline drops can be directly instilled in the nasal cavity to keep nasal secretions fluid and enhance clearance to the nasopharynx. Owners can instill 1 drop in each nostril once daily, using a dropper or syringe. Topical decongestants are vasoconstrictors that act on the capacitance vessels in the turbinates. These can shrink the nasal mucosa, open the ostia to the frontal sinuses, and facilitate sinus and nasal cavity drainage. Phenylephrine (0.125%) or oxymetazoline (diluted to 0.025%) can be administered at a rate of 1 drop in each nostril once daily. Topical decongestants should not be used for more than three consecutive days, as this can cause a rebound vasodilation and nasal congestion. For cats experiencing severe nasal airway obstruction, intermittent nasal flushing under anesthesia can help to clear the nasal airways, facilitate mucociliary clearance, and enhance the efficacy of antiinflammatory and antimicrobial therapy. Finally, analgesics should be considered in cases with bony involvement (invasive nasal tumors, rhinitis with osteomyelitis) or to ameliorate post-biopsy pain. The injectable form of buprenorphine can be administered sublingually at 5–10 µg/kg up to every 6 hours. Tramadol can also be used in cats for nasal or bone pain at 2–4 mg/kg BID.
SUMMARY
While referral to specialty practice will always be an option, thorough diagnostic evaluation for chronic nasal disease can be done in most practice settings, and it may not always require specialized diagnostics. Practitioners should be comfortable recognizing opportunities to provide definitive therapy, empirical therapy, and symptomatic therapy for these patients.

REFERENCES
Cigarette Smoke and the Family Pet
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INTRODUCTION
Exposure to indoor air pollutants represents a significant health risk to people. Of particular concern are the health risks of exposure to people with preexisting respiratory disease and exposure to children. Because of the nature of their body size and lifestyles, indoor pets - particularly those with respiratory disease - may be even more vulnerable to the harmful health effects of indoor air pollutants. This session will review the anatomic and functional aspects of the companion animal respiratory system that make it vulnerable to air pollution-induced injury. Using environmental tobacco smoke (ETS) as an example, this session will review studies that document pathologic and functional repercussions of indoor air pollutant exposure in pets. Finally, this session will review the recommendations for reducing indoor air pollutant exposure in people, and discuss potential applications of these strategies for companion animals.

THE RESPIRATORY SYSTEM AND AIR POLLUTION
The nose not only serves as the principal organ for the sense of smell, but it also functions to efficiently filter, warm, and humidify the inhaled air before it enters the more delicate distal tracheobronchial airways and alveolar parenchyma of the lung. With its role as an “air conditioner” and a “defender” of the lower respiratory tract, the nose may also be vulnerable to acute or chronic injury caused by exposure to toxic air pollutants. A wide range of xenobiotics in the air could potentially cause nasal responses that would compromise respiratory health. The lower respiratory tract is designed to efficiently exchange gases between the ambient air and the pulmonary circulation. To achieve this goal, the pulmonary parenchyma is extremely thin and delicate and is repeatedly or chronically exposed to airborne xenobiotics, rendering the lower respiratory tract similarly vulnerable to injury from air pollutants.

Epidemiologic evidence suggests that children may be more vulnerable to the harmful health effects of air pollutants. Proposed mechanisms for this increased vulnerability include higher minute ventilation per unit bodyweight, longer periods of exposure to pollutants, and a lower breathing zone - potentially resulting in longer exposures to higher concentrations of pollutants. These same pathophysiologic mechanisms can also be applied to companion animals, in particular to indoor pets and their risk of exposure to indoor air pollutants.

ENVIRONMENTAL TOBACCO SMOKE AND THE FAMILY PET
Environmental tobacco smoke (ETS) is the combination of cigarette smoke from two sources. Sidestream smoke is the smoke emitted from the end of a burning cigarette, cigar, or pipe. Mainstream smoke is the smoke inhaled (sometimes through a filter) and exhaled by the smoker. More than 4000 compounds have been identified in ETS, including carcinogens, tumor promoters, and potent oxidants. Respiratory effects of ETS in people include induction of acute lower respiratory infections, induction and exacerbation of asthma, and induction of middle ear infections.

Several studies have documented exposure of companion animals to ETS in their households. Elevated concentrations of cotinine, a metabolite of nicotine and a biomarker of ETS exposure, have been detected in the urine of cats and dogs from homes with cigarette smokers, compared to animals from homes without smokers. Dogs exposed to cigarette smoke had elevated macrophage and lymphocyte cell counts in bronchoalveolar lavage fluid compared to nonexposed dogs. Anthracosis has been detected in the alveolar macrophages of both dogs and cats from smoking households.
The health effects of ETS exposure in companion animals have also been investigated. A recent study by Rozanski et al. found that dogs exposed to ETS had higher expiratory airway resistance and decreased functional residual lung capacity compared to nonexposed dogs. Epidemiologic studies found a higher risk of lymphoma in ETS-exposed cats and higher risks of nasal and paranasal sinus tumors in ETS-exposed dogs.

**IMPROVING INDOOR AIR QUALITY - WHAT TO TELL CLIENTS?**

The Environmental Protection Agency establishes and updates guidelines for improving indoor air quality, with goals set to protect vulnerable populations, including children and people with respiratory disease. Many of these guidelines are relevant to reducing exposure risk to companion animals and should serve as a starting point for the reduction of indoor air pollutant-related health risks for our patients.

**Environmental Tobacco Smoke**

The Surgeon General has concluded that there is no risk-free level of exposure to ETS. Furthermore, residues from ETS can remain on surfaces and react with other indoor and outdoor oxidant pollutants, generating additional toxic gases and particulates that may be more toxic than the original compounds. Because these residues can persist for months, this concept of “third-hand smoke” exposure may prolong the risk of health effects long after the smoking took place. For these reasons, the only way to protect pets from the potential health effects of ETS is through a 100% smoke-free environment.

**Other Strategies**

Ventilating rooms helps reduce concentrations of indoor pollutants. When weather and outdoor pollutant levels permit, open windows and doors or use whole-house ventilation systems to help remove pollutants from the indoor environment. Changing filters in central air conditioning and heating units can help reduce dust and other particulate pollutants. Maintain indoor relative humidity between 30% and 50%. Air that is too dry may be directly irritating to the airway mucosa, while air that is too damp may promote the growth of mold - a potential trigger for asthma and rhinitis.

**REFERENCES**

What’s That? Acquiring the Complete Pediatric Abdominal Ultrasound Scan
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Small animal patients are commonly presented to the veterinarian because of signs referable to the abdominal cavity due to congenital anomalies, dietary indiscretion, parasitic infestation and infectious or inflammatory disease. Abdominal ultrasound provides valuable clinical information about the peritoneal cavity, great vessels, abdominal viscera and lymph nodes obtained in a noninvasive fashion, with no confirmed adverse biologic effects, and usually not necessitating sedation or anesthesia. This paper reviews the techniques for performing a complete pediatric abdominal ultrasound scan.

Abdominal ultrasound provides useful data in a short period of time. The normal paucity of intraabdominal fat in pediatric patients results in less informative abdominal radiography, but actually improves ultrasonographic imaging. (Abdominal fat attenuates the ultrasound beam.) Image quality is improved with small patient size as a higher frequency scanhead can be employed. Acquisition of special equipment for pediatric ultrasonography is usually not necessary, as scanheads selected for small animal (especially feline) clinical use are appropriate for most pediatric cases.

Small animal patients are best evaluated using an ultrasound machine equipped with a curvilinear variable frequency scanhead (6.0–8.0 MHz). Many portable machines now have available a high-frequency linear scanhead (8.0–10.0 MHz), which will improve quality and also allow evaluation of smaller regional anatomy (thyroid, parathyroid, cryptorchid testes).

Preparation
The small animal patient should be placed in dorsal recumbency within a padded V-trough and gently restrained by assistant(s) holding the forelimbs and hind limbs. Sedation is rarely required for the basic abdominal scan unless marked pain or apprehension is present. Allowing the patient to become accustomed to this restraint before initiating clipping or scanning usually minimizes struggling and resultant aerophagia.

Clipping the craniocentral abdominal hair using a No. 40 blade and wetting the skin with water, tincture of zephiran or 70% isopropyl alcohol, followed by a liberal amount of ultrasound gel permits the best acoustic coupling of the scanhead to the patient, improving the image obtained. Some pediatric patients have scant ventral hair coats and will not require clipping. Care should be taken to avoid excessive chilling of pediatric patients secondary to the application of room temperature liquids followed by evaporation. Electric warming devices (warm water blankets) may cause electronic interference with the ultrasound equipment; warm water bottles or their equivalent are superior.

Fasting as much as is safely possible in the small animal patient minimizes gastric ingesta obscuring imaging of the liver and gastrointestinal gas accumulation interfering with visualization of other abdominal viscera. Preventing urination immediately prior to the examination permits better evaluation of the urinary bladder.

Serial evaluations can provide useful information when the clinical status of the small animal patient has changed; clinicopathologic deterioration, progressive lethargy or obtundation, acute pain, changes in abdominal palpation findings or refractory vomiting or diarrhea warrant repeat evaluation for ultrasonographic signs indicating intussusception, perforation and/or peritonitis have evolved.

The Normal Abdomen
Regardless of the clinical history, the abdomen should be evaluated methodically with the animal in dorsal recumbency. Place the scanhead under the xiphoid with the beam in sagittal plane. Visualization of the liver is achieved by fanning the beam from right to left. The gall bladder is seen on the right; the
left liver lobes are seen ventral and sometimes caudal to the stomach. Turning the beam to transverse allows for visualization of the liver between stomach and gall bladder. This view is good for evaluation of the hepatic border, echogenicity of hepatic parenchyma and portal architecture. The portal vessels have very y echogenic walls.

Resuming the sagittal plane, scan to the left of the dog past the stomach to the spleen. The spleen will be visualized ventrally in the near field. Splenic border, parenchyma and shape should be evaluated. Following the spleen transversely down the left body wall, you will see the left kidney.

Once visualization of the kidney is achieved, turn to the sagittal plane and evaluate the renal border, cortical echogenicity and pelvic architecture. Dilatation of the renal pelvis is best seen in the transverse plane. The adrenal is located medial to the cranial pole of the kidney. In sagittal, maintaining strong hand pressure, scan medially to visualize the linear aorta and the renal artery. The left adrenal is located cranial to the left renal artery and caudal to the left cranial mesenteric artery. The left adrenal is visualized as a bi-lobed structure with the phrenicoabdominal vein at its waist.

With a transverse beam back in the middle of the abdomen, scan caudally to a large hypoechoic structure, the urinary bladder. Evaluate bladder wall and lumen contents, and, dorsal to the bladder, the major vessels (caudal vena cava and aorta). Sublumbar lymph nodes will be seen at the aortic bifurcation into the iliac arteries, adjacent to the bladder wall. Sagittal scanning of the urinary bladder caudally will allow visualization of the urethra (and prostate in the male).

At the edge of the right ribcage at the renal fossa of the liver, the right kidney will be found. The right kidney should be evaluated as was the left (renal border, cortical echogenicity and pelvic architecture). By scanning sagittally between the right kidney and the caudal vena cava with a fanning technique, the right adrenal is visualized just lateral to the caudal vena cava. In transverse, find the right kidney, and lateral to the kidney, the duodenum.

At the cranial end of the kidney medial to the duodenum will be the right limb of the pancreas. The right pancreatic limb is identified by visualizing the caudal pancreaticoduodenal vein within the structure. Turning to the sagittal plane, follow the pancreas, scanning medially to the angle of the body and left limb, or sagittally scan the caudal border of the stomach. The pancreatic body is seen caudal to the stomach, cranial to the splenic vein. The left limb is found caudal to the splenic vein and midline to the cranial pole of the left kidney.

Returning to the transverse plane in mid abdomen at the mesenteric root, scan for mesenteric lymph nodes and small bowel wall changes. It may take 2–3 passes to evaluate the entire abdomen scanning in a uniform serpentine fashion.
Abnormal Pediatric Abdominal Ultrasound/Case Studies
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Pediatric patients are commonly presented to the veterinarian because of signs referable to the abdominal cavity due to congenital anomalies, dietary indiscretion, parasitic infestation and infectious disease. Abdominal ultrasound provides valuable clinical information about the peritoneal cavity, great vessels, abdominal viscera and lymph nodes obtained in a noninvasive fashion and usually not necessitating sedation or anesthesia. Ultrasonography thus greatly facilitates diagnostic differentiation between congenital and acquired disorders; techniques will be described in this paper.

Disorders of Urogenital Development
Veterinary pediatric ultrasonography has been hampered by the small size of neonatal organs, but advances in pediatric veterinary ultrasonography have been encouraging. Abdominal ultrasound can facilitate the diagnosis of congenital urogenital disorders, because ectopic, distended ureters and changes in renal architecture are usually readily seen. The presence and location of cryptorchid testes can often be detected with ultrasound. Ultrasonographic examination of the bladder disclosing urolithiasis can provide information suggesting congenital hepatic vascular anomalies.

The most common familial disorders in cats and dogs include renal agenesis, renal dysplasia, polycystic kidneys, renal amyloidosis, basement membrane disorders, and tubular dysfunction (Fanconi’s syndrome).

Renal Agenesis
Congenital renal agenesis resulting in the absence of a kidney can be confirmed with ultrasound. The contralateral kidney typically has normal internal anatomy, but is enlarged as a consequence of obligatory hypertrophy. Renal function of the pediatric patient does not equate that of the adult until 4–6 months of age; compensatory renomegaly may not be apparent until that time.

Renal Dysplasia
Until reliable genetic markers are available for the various breed-specific congenital renal dysplasias, ultrasound provides the best method of screening young dogs and cats for these likely heritable disorders. Early ultrasonographic screening is possible in platycephalic breeds in which morphologic changes are grossly evident (i.e., Persian cats, Cairn terriers, German Shepherd dogs).

Ectopic Ureter
Congenital ectopic placement of the distal ureter into the urethra, vestibule or vagina is usually associated with ureteral dilation with or without renal pelvic dilation. Dilation of the ureter improves the sensitivity of the ultrasound study; however, the diagnosis can be elusive. Visualization of a nonvascular fluid-filled structure with a hyperechoic wall passing dorsal to the urinary bladder, or obvious insertion of the structure into the proximal urethra suggests the diagnosis. Visualization of the ureteral jets in the bladder suggests normalcy; however, some ectopic ureters insert initially into the bladder and additionally tunnel distally to terminate in an abnormal site. Visualization of the dilated ureter usually occurs near the urinary bladder. Visualization of the bladder neck and proximal urethra may be obscured by pubic bone, making identification of such termination difficult.

Hydronephrosis can eventually result from an uncorrected ectopic ureter due to flow impedance at the abnormal site of insertion. Urinary tract infection is commonly associated with ectopia, due to accompanying urethral sphincter mechanism anomalies, and if not detected and treated can progress to
pyelonephritis and ureteritis. Infection and its associated inflammation in the tract can further alter the ultrasonographic appearance of the kidneys, bladder, ureters and urethra (see below).

Contrast-enhanced computed tomography is the most sensitive and specific modality for the diagnosis of ectopia, but, like double contrast radiography, requires anesthesia, making initial evaluation with ultrasound desirable when ectopia is suspected clinically. The condition is thought to be heritable and is more common in females.

Ureterocele
A ureterocele is an uncommon congenital dilatation of the ureter near the bladder, appearing as a cystic structure within the bladder lumen or wall. The ureterocele occurs most commonly in association with an ectopic ureter. Diagnosis can be made by scanning the urinary bladder in the transverse plane and watching for strong peristalsis of the adjacent ureter.

Patent Urachus
The urachus permits the flow of urine from the bladder into the allantoic sac of the fetus, and normally atrophies at birth. A patent urachus in the neonate is characterized clinically by urine dribbling from the umbilicus. The fluid-filled urachus can be identified ultrasonographically, extending cranially from the cranioventral bladder wall. If an incompletely patent urachus is present in the neonate, a urachal diverticulum may result, seen as a divot in the apex of the bladder. Urachal diverticula can predispose the bladder to recurrent infection because of abnormal bladder flow in the region; surgical excision can be indicated.

Cryptorchidism
Ultrasound localization of cryptorchid testis(es) can confirm the condition in pediatric patients with bilateral involvement whose neutering status is unknown, and assist the surgeon in planning the approach (i.e., inguinal vs. cranial abdominal). The retained testis can be positioned anywhere between the ipsilateral kidney and the scrotum. A systematic evaluation of the region from the caudal renal pole to the inguinal canal can identify an oval, homogeneously echogenic structure with a mildly hyperechoic border representing the parietal and visceral tunics. The epididymis is usually distinctly less echoic than the testicular parenchyma, as in the scrotal testis. The cryptorchid testis will maintain the anatomic structure, the median testes (a hyperechoic slash), and normal testicular echogenicity despite being reduced in size as compared to a scrotal testis.

Ultrasound is also the test of choice to detect non-descended testicles in adult dogs and cats. Ultrasound may also detect nonpalpable testicular tumors, which are more prevalent in this group of patients.

DISORDERS OF THE DIGESTIVE SYSTEM DEVELOPMENT

Hernia
Congenital peritoneopericardial diaphragmatic hernias occur in both the dog and cat; ultrasonography provides an additional modality for their diagnosis. As with other diaphragmatic hernias, careful evaluation for continuity of the echogenic diaphragm differentiates a true hernia from mirror image artifacts. Evaluation of the pericardial contents can be made from the subcostal (across the liver) or intercostal (using the heart as an acoustic window) approach. Abnormal pericardial contents can include falciform fat, liver, gall bladder and/or intestines. Congenital inguinal hernias can similarly be confirmed by ultrasonographic identification of intestines in the subcutaneous space of the affected groin. This can be a dynamic finding. Mesenteric fat may alternatively be entrapped through the hernia.

Congenital hiatal hernias are more difficult to confirm with ultrasound because of the inherent difficulty imaging the gas-filled stomach and the intermittent nature of the disorder. Stomach wall with
characteristic rugal folds can be imaged crossing the diaphragm into the thoracic cavity. Fluoroscopic evaluation can be more informative in these cases.

A developmental anomaly resulting in extrusion of a portion of the gastrointestinal tract outside of the body wall, occurring within the umbilical canal (omphalocele) or lateral to the umbilical canal (gastroschisis), has been reported in humans and occurs in both dogs and cats. The condition is usually hopeless in small pediatric patients presented to the veterinarian hours after birth; however, a 30–70% survival rate is reported in humans with immediate postpartum surgical intervention. Diagnosis is made prepartum with abdominal ultrasound, based on the recognition of fetal gastric wall (rugal) structures or intestinal contents in an abnormal location. Earlier surgical intervention before inevitable septic contamination occurs may improve the prognosis in veterinary patients.

**Enteric Anomalies**

Pyloric stenosis secondary to hypertrophic gastritis has been reported in a pediatric dog. Focal circumferential thickening of the pylorus primarily involving the muscularis is typical.

Enteric duplication or agenesis can be confirmed ultrasonographically in pediatric patients. Duplication is rare and can occur anywhere in the intestinal tract, and the clinical signs may be nonspecific. A fluid-filled juxtaintestinal formation with variable peristalsis and contents can be seen. Enteric agenesis usually results in severe clinical signs in the neonatal period. Ultrasonographic findings usually include marked fluid and gas distention of bowel proximal to the defect.

Several breeds of dogs have a reported genetic predilection to small intestinal disease. Normally, the small bowel appears sonographically as four distinct layers. The bowel lumen is hyperechoic, as gas and ingesta are compressed. The layer just outside the lumen is the mucosa; it is hypoechogenic and normally the thickest-appearing section. Outside the mucosa is the submucosa; it is hyperechoic to the mucosa and about one-third the thickness. The muscularis, the bowel muscle layer, is outside of the submucosa and appears as a very thin, hypoechogenic black line. An immunoproliferative enteropathy is seen in the Basenji breed, which is characterized by lymphangiectasia, intermittent diarrhea, weight loss, hypoalbuminemia and hyperglobulinemia, and lymphoplasmacytic mucosal infiltrates throughout the GI tract. Histopathology is diagnostic; however, abdominal ultrasonography can identify bowel in which disruption of the normal layering has occurred. Chinese Shar-Pei dogs have been identified with a lymphoplasmacytic-eosinophilic infiltrative enteropathy that is characterized by poor weight gain, weight loss, or intermittent diarrhea episodes, with onset of signs typically between 2 and 6 months of age. Infiltrative enteropathies can be characterized ultrasonographically as having changes in the normal bowel wall layering.

**Portosystemic Shunt**

Portosystemic shunts (PSS) are congenital malformations of the hepatic portal venous drainage system and can have either a familial (i.e., genetic) or random occurrence. Congenital PSS can be either intrahepatic or extrahepatic; breed predilections for extrahepatic shunts include Yorkshire terrier, Maltese, Poodle, Miniature Schnauzer, Dachshund, Lhasa Apso, Pekingese, Pug, and Shih Tzu - whereas intrahepatic shunts are more commonly identified in large-breed dogs such as Golden Retrievers, German Shepherds, Irish Wolfhounds, Irish Setters, and Samoyeds. PSS are uncommon in cats.

Ultrasonography provides a rapid and noninvasive method for screening patients suspected to have congenital portosystemic shunts. Although scintigraphy (transcolonic portal scintigraphy or transplenic portography) is considered the most reliable noninvasive method of documenting a portosystemic shunt, its availability is limited to specialty and university practices, and its use dictates special handling of the radioactive patient for at least 12 hours. Mesenteric portography, although more invasive and requiring general anesthesia, is a highly reliable method of confirming and localizing PSS.
Abdominal ultrasonography is a useful diagnostic and is routinely done when PSS is suspected. It is noninvasive and requires no anesthesia; however, diagnostic accuracy is highly operator-dependent, and the PSS will be confirmed in only approximately 60–80% of cases. The liver may be small and difficult to image in patients with congenital portosystemic shunts. Imaging the liver from the standard ventral approach can be improved in some cases by using the left ventral intercostal and right dorsal intercostal approaches. The presence of ascites can facilitate the study, as can adding fluid to the stomach and positioning the patient to shift gas away from the scanhead and shift abdominal organs caudally. Ultrasound evaluation of portosystemic anomalies can be facilitated by positive-pressure ventilation under anesthesia for the same reason.

Postoperatively, ultrasound can be used to evaluate portal blood flow following surgical banding or coil embolization. Extrahepatic shunts most commonly arise from the portal vein, splenic vein or left gastric vein in the dog and from the left gastric vein in the cat. Identification of a shunting vessel emptying into the caudal vena cava is difficult but confirmatory. Intrahepatic shunts can be more difficult to identify because of patient size, bowel gas, and liver size. Clipping the hair coat intercostally on the right can allow for transverse vessel stacking (of the aorta, vena cava and portal vein) and allow visualization of ductal shunts. There can be right and left shunting of the ductus.

Reproductive Disorders of Neutered Dogs (for DVMs Who Don’t Want to Do Reproduction)
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Despite the fact that the majority of client-owned pets in the USA are neutered, veterinarians are commonly confronted with disorders of the (residual) genitourinary tract.

PUPPY “VAGINITIS”
An apparently healthy female puppy is presented with mucoid vulvar discharge, usually white to yellow, and sometimes copious. The discharge can be accompanied by mild perivulvar dermatitis. The puppy is not typically attentive to the discharge, and there is not any associated change in urinary behavior (dysuria or pollakuria). Clients often have a difficult time deciding if a puppy has normal urinary behavior or not. The age of onset ranges from 6 weeks to puberty, the duration days to months, and the disorder often intermittent. Cytologic examination of the discharge is suppurative. Vaginal cultures (aerobic) generally fail to grow anything but normal flora in small, mixed numbers. Similar organisms could be cultured from an asymptomatic littermate. A urinalysis, acquired by cystocentesis, is characteristically normal (a decreased urine specific gravity is typical for young dogs lacking adult concentrating abilities), and urine culture, if performed, is negative. The clinician needs to perform enough diagnostics to rule out more significant causes of vulvar discharge and feel comfortable with the diagnosis of benign puppy vaginitis.

The specific etiology of puppy vaginitis is unknown. An imbalance of juvenile vaginal glandular epithelium is postulated. The condition is reported in the literature to resolve both with puberty and with ovariohysterectomy - two very different events endocrinologically; therefore, neither is likely to truly cause resolution. Puppy vaginitis diminishes with maturity. The term is a misnomer, as it is asymptomatic and not inflammatory. Important rule-outs (some of which are associated with inflammation) include urinary tract infection, urine scalding, perivulvar dermatitis, the onset of the initial estrous cycle, vaginal foreign bodies (i.e., foxtails) and urogenital anatomic anomalies (ectopia, disorders of sexual differentiation, significant strictures).

Cleansing the perivulvar area with a gentle solution (nonalcoholic otic preparations or “baby wipes”) and benign neglect and tincture of time are advised.
**CHRONIC VAGINITIS**

Bitches present with variable vulvar discharge, which is mucoid to hemorrhagic or purulent and usually accompanied by signs of discomfort (licking, scooting, pollakiuria). Perivulvar and vulvar dermatitis are also frequently present. The condition is invariably seen in ovarietomized bitches of any age, and at variable times from the spay procedure. The history usually includes multiple therapeutic efforts without resolution, although transient improvement can occur. The duration is generally chronic, from weeks to months and sometimes lasting years.

The etiology of chronic vaginitis is usually multifactorial, and the primary cause often masked and exacerbated by previous therapies, including long-term antimicrobial use, self-mutilation and topical irrigations. Vaginal mucosal biopsy frequently shows nonspecific lymphoplasmacytic inflammation, but sometimes suppurative (neutrophilic) or eosinophilic inflammation is predominant. Vaginal cultures can show overgrowth of an atypical bacterial species (pure Gram-negative cultures, resistant organisms, *Pseudomonas* spp.) or pure culture of *Mycoplasma* spp. if antibiotics have been used extensively. Occasionally, a yeast overgrowth is identified. Primary bacterial vaginitis is rare.

The most common documented etiologies of chronic vaginitis at the VMTH include:

1. Extensive perivulvar dermatitis associated with redundant dorsal and lateral vulvar folds
2. Granulomatous uterine stump (rule out stump pyometra)
3. Vaginal foreign bodies (foxtails, bone fragments)
4. Chronic urinary tract infection with urethritis/vestibulitis/vulvitis
5. Cystic, urethral, vaginal or vestibular neoplasia
6. Vaginal strictures are commonly identified but unusually causal in this author’s opinion
7. Most cases are idiopathic

A minimum database should be performed on these chronically affected bitches, involving a CBC and serum chemistries. Urinalysis (preferably acquired by cystocentesis) with culture (if indicated) is advised. A careful vaginal examination under adequate (heavy) sedation or anesthesia, with endoscopic equipment allowing evaluation of the entire vaginal vault, should be performed. This usually means a rigid cystourethroscope with saline infusion is a necessity. Otoscopes and vaginal speculums do not permit adequate evaluation of the entire vaginal vault. Pediatric proctoscopes lack the sensitive optics of cystoureoscopes.

Radiography (vaginogram/urethrogram/cystogram/IVP) and/or ultrasound of the entire genitourinary tract can be helpful in localizing the problem and eliminating differentials. Ultrasound is preferable as it does not require anesthesia.

Vaginal cytology, aerobic and *Mycoplasma* guarded vaginal cultures, and pinch biopsy of affected vaginal mucosa may be helpful in better defining the problem. Identification of any contributory anatomic abnormalities is important (significant strictures, mass lesions, redundant dorsal vulvar folds, anomalous ureteral anatomy). It is helpful to evaluate the bitch in a normal standing position to accurately assess external anatomy (redundant folds?), followed by another examination after she has urinated, and again after recumbency (urine pooling and scalding?). The presence of urine pooling in the vaginal vault, noted only when the bitch is under anesthesia, can be misleading; the presence of redundant vulvar folds is difficult to ascertain when the bitch is positioned for vaginoscopy.

General guidelines apply to most cases: the discontinuation of topical irrigations, prevention of self-mutilation with Elizabethan collars, and initiation of antimicrobial therapy only when indicated by proper interpretation of culture and sensitivity testing should be undertaken. Antimicrobial therapy should be limited to those cases where pathogens have been identified as displacing normal flora. Analgesia and antiinflammatory therapies are indicated in many cases. A short antiinflammatory course
of corticosteroids can be useful in diminishing vaginal inflammation, but the subsequent propensity for urinary tract infection must be kept in mind, and problems with long-term use limits usefulness. Nonsteroidal antiinflammatories are therefore superior. Narcotics may be necessary for adequate analgesia (Tramadol).

If a specific cause is identified, resolution is more straightforward. Surgical correction with careful postoperative control of self-mutilation is indicated if anatomic abnormalities (redundant dorsal vulvar fold, significant vaginal stricture, granulomatous uterine stump) have contributed to or caused the condition. Obviously the identification and removal of foreign bodies should cure chronic vaginitis. Appropriate management of chronic urinary tract infection, if identified, should resolve associated vaginitis. Therapy of urogenital neoplasia can include surgery and/or chemotherapy.

If the condition is idiopathic (no anatomic, foreign body, infectious, granulomatous or neoplastic cause can be discerned), oral estrogen replacement therapy is often helpful in establishing normal mucosal integrity and eventual normalization of the vaginal vault. The condition is likely similar to postmenopausal vaginitis in women secondary to low estrogen levels. Women improve with vaginal estrogen application, difficult in the dog. Oral diethylstilbestrol (compounded) (“DES”) is therefore advised; the dose is empiric and usually the same as what is used for urinary incontinence due to sphincter incompetence. Several weeks of therapy with DES may be required before improvement is recognized. Side effects are uncommon: mild overdosage results in signs of proestrus (attraction to male dogs, vulvar swelling); myelosuppression is highly unlikely if dosage is conservative (i.e., 60-lb dog would receive 1 mg once or twice weekly).

**Ovarian Remnant Syndrome/Hyperestrogenism**

Ovarian remnant syndrome causes the presence of behavioral and/or physical signs of estrus in a female dog or cat having previously undergone ovariohysterectomy (OHE). It is caused by the presence of functional residual ovarian tissue. The ovarian remnant syndrome is reported to be responsible for 17% of all post-OHE complications. It occurs in female dogs and cats and is more common in cats. No breed predisposition or geographic distribution has been reported. The signs of estrus usually occur months to years after OHE, but can begin within days after surgery. In bitches, signs reported include attraction of male dogs, swelling of the vulva, mucoid to sanguineous vaginal discharge, passive interaction with male dogs, flagging, and some even allow copulation. The signs of proestrus last an average of 9 days; signs of estrus last an average of 9 days; the average interval between signs of estrous cycles is 7 months. Of note, the signs are usually cyclical or periodic (i.e., q 6 months) rather than constant.

In queens, signs reported include vocalization, lordosis, restlessness, head rubbing, rolling, tail deviation and treading the hind limbs; the queen may allow copulation. Queens demonstrate typical behavioral signs of estrus in a cyclical (seasonally polyestrus) fashion. Estrus lasts 2–19 days, followed by an interestrus interval that lasts for 8–10 days unless ovulation and luteinization occurred, in which case the interestrus interval is at least 45 days.

The most common cause is a previous failure to remove both ovaries completely. There is no correlation with age at OHE, difficulty of surgery, obesity of patient, or experience of surgeon (reportedly). The presence of anatomically abnormal ovarian tissue (fragmentation into the broad ligament) is possible but uncommon, and a supernumerary ovary is very rare. Experimentally, functionality returns to ovarian tissue removed from its vascular supply and replaced into or onto the lateral abdominal wall.

The clinician needs to consider multiple differentials, including inflammation or infection of the genitourinary tract, vaginal hemorrhage due to foreign body, trauma, a uterine stump granuloma or pyometra, neoplasia of the genitourinary tract, vascular anomalies of the genitourinary tract, a
coagulopathy, exogenous estrogen administration (this one is important!) and an endogenous extraovarian source of estrogen: adrenal pathology (rare).

A minimum database including a CBC/biochemistry/urinalysis with culture should be performed. They are usually normal, but can show chronic blood loss anemia if vaginal hemorrhage is profound; this is uncommon unless concurrent ovarian neoplasia, follicular cysts, coagulopathy, or other systemic disease exists. Pancytopenia is possible from estrogen toxicity. Critical observation of behavioral and physical signs of estrus together with vaginal cytology and/or measurement of serum progesterone or estradiol concentrations can confirm the presence of functional ovarian tissue. Vaginal cytology will identify estrogen effect: vaginal mucosal cornification is a bioassay for elevated plasma estradiol concentrations. Recall that vaginal cytology in the bitch shows epithelial cell cornification generally > 90% during estrus (superficial and pyknotic or anuclear cells). Vaginal cytology in the queen shows epithelial cell cornification ranging from 10–40%, and clearing (absence of debris and clumping of cells) occurs in 90% of smears during estrus.

A serum progesterone concentration > 2 ng/mL (measured 1–3 weeks after behavioral estrus) is consistent with functional luteal tissue. GnRH (50 μg IM), hCG (400 IU IV), or hCG (1,000 IU “1/2 IV, 1/2 IM”) can be used to attempt to induce ovulation or luteinization for diagnostic purposes; serum progesterone concentration is measured 2–3 weeks later; this is often unrewarding due to the refractory nature of the ovarian remnant. In the queen, if ovulation or luteinization is stimulated during behavioral estrus, and serum progesterone concentration is measured 2–3 weeks later, post-stimulation serum progesterone concentrations > 2 ng/mL are consistent with adequate coital stimulation and functional luteal tissue. GnRH (25 μg IM) can be used to attempt to induce ovulation or luteinization for diagnostic purposes; serum progesterone concentration is measured 2–3 weeks later, but this again can be unrewarding. Note that peak estradiol levels triggering behavioral estrus range from 20 to > 70 pg/mL; however, vaginal cytology closely correlates with serum estradiol and is much less expensive to perform.

Ultrasound can be used to support a diagnosis of ovarian remnant syndrome that is based on history, clinical signs and vaginal cytology. Imaging should begin in a sagittal plane slightly caudolateral to the kidneys (where remnant ovarian tissue is expected). Remnant ovarian tissue may be visible only during the follicular phase (anechoic, cystic structures) or the luteal phase (hypo or isoechoic cystic structures). Ectopic ovarian tissue can be difficult to locate and image using ultrasonography and often requires operator expertise, but it contributes significantly to the diagnosis and makes the proposal of a laparotomy a much more comfortable one. The adrenal glands should be evaluated at the same time for normal size and shape.

Exploratory laparotomy with the goal of removal of residual ovarian tissue confirms and resolves the problem. The identification of residual ovarian tissue is facilitated by the presence of active follicles or resultant corpora lutea; the clinician should schedule the surgical procedure during times of elevated progesterone or during behavioral estrus. All visible ovarian tissue should be revised and evaluated by histopathology; however, if no visible ovarian tissue is identified, all residual tissue at the ovarian pedicles should be resected and submitted for histopathology. Removal of functional luteal tissue may induce transient signs of pseudopregnancy in dogs and cats postoperatively. If profound, anti-prolactin therapy (cabergoline) can be offered. Successful removal of remnant ovarian tissue should result in cessation of clinical signs of estrus.

Medical therapy is often requested by clients not eager to permit another surgical procedure. Progestational or androgenic compounds used to suppress follicular ovarian activity are not recommended because of undesirable side effects (mammary neoplasia, diabetes, undesirable behavior). Immunocontraception or GnRH agonist administration will offer a viable alternative to laparotomy when perfected and commercially available.
Compounded, Generic, Patented and Pirated Drugs: Are They Really Any Different?
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INTRODUCTION
Veterinarians writing a prescription or dispensing a drug for a patient assume responsibility for the medical treatment of that animal. More and more clients are choosing to purchase veterinary drugs from alternative sources such as online or human pharmacies. Therefore, veterinarians need to be able to help their clients make wise choices about where to buy drugs and what products to choose. Veterinarians also need to be able to clearly articulate when there is an advantage to buying a drug directly from the clinic versus the “better deal” on the Internet. Finally, veterinarians must be able to ensure that their clinic is purchasing and dispensing safe and efficacious products. The first step is to understand the legal, safety and quality differences between patented, generic, compounded and pirated drugs.

REGULATION OF PHARMACEUTICALS IN CANADA
The manufacturing of veterinary pharmaceuticals in Canada is under federal jurisdiction. The Veterinary Drugs Directorate (VDD) is part of the Health Products and Food Branch of Health Canada. The VDD scrutinizes all applications by drug manufacturers to market new products in Canada, sets standards, and promotes the prudent use of veterinary drugs in food-producing and companion animals. A list of all drugs that are licensed for sale in Canada is available on the Canada VDD Drug Product Database: www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

The sale and compounding of drugs is under provincial/territorial jurisdiction. It is regulated by both pharmacy and veterinary professional regulatory bodies, and the rules and enforcement can vary among provinces and territories.

Patented Drugs
Companies manufacturing pharmaceuticals in Canada must comply with the federal Food and Drugs Act and Regulations. Health Canada scrutinizes all new drug submissions for efficacy, safety and quality by examining the results of drug trials. This process is estimated to cost pharmaceutical companies $40–50 million and take at least five years for each product. Why so expensive? Companies must first discover, purify, characterize and then test a chemical. Over 1000 chemicals may be tested for each one that goes on to clinical trials. The trials consist of in vitro preclinical studies examining varying doses to obtain preliminary data on efficacy, toxicity and pharmacokinetics. The drugs are then put through rigorous clinical trials such as microdosing and dose escalation studies in healthy animals to assess the basic pharmacokinetics. Next, larger groups of animals are treated to assess efficacy and safety. If these
studies are successful, then the product enters multicentre trials that compare the product to a gold standard of treatment.

Drugs that pass this careful scrutiny are given a drug identification number (DIN) indicating the right to mass produce and market a drug in Canada. If it is a patented product, the company is also given exclusive rights to sell the product in Canada for 20 years. All fabricators, packagers, labelers, distributors, importers, testers and wholesalers involved in the production and marketing of each drug must obtain an establishment license (EL) and meet the standards of good manufacturing practices (GMP).¹

Patented products are manufactured under rigid guidelines and must be closely monitored for quality, safety and efficacy. The companies must also continue with ongoing pharmacovigilance once a drug is being sold to ensure that any unexpected adverse reactions or intolerable long-term effects are documented. If pharmacovigilance reveals unexpected or unacceptable toxicity, then the labels may change or a drug may even be recalled or withdrawn from the market.

Patented drugs are sometimes perceived as expensive; however, they have been and continue to be rigorously tested for quality, safety and efficacy, and they are manufactured under strict guidelines.

**Generic Drugs**

Other companies can apply to produce and market a product as a generic drug when the patent of a pioneered drug expires. This is also overseen by the VDD, which uses the guidelines in “Preparation of Veterinary Abbreviated New Drug submissions: Generic Drugs.” These guidelines contain safety, manufacturing, and chemistry requirements in addition to pharmacological and statistical principles.³

Generic drug manufacturers must demonstrate that their product is bioequivalent to the patented product, called the Canadian Reference Product (CRP). This means that their product is pharmaceutically equivalent (has the same strength, potency, quality, purity, content uniformity, disintegration and solubility as the CRP) and has the same bioavailability. Because there is a chance that the bioavailability (absorption) of a generic product could be different, the manufacturer must demonstrate that the product has a similar rate and extent of absorption within predetermined limits under similar experimental conditions.³ The excipients (inactive ingredients), however, can be different provided that they do not affect absorption.³

Companies that produce a generic pharmaceutical do not need to do safety and efficacy studies, because demonstrating bioequivalence to a CRP implies that efficacy and safety have already been proven. This saves millions of dollars and years of testing and is why generic products are less expensive than the original product.

Other than not having to repeat the safety and efficacy studies, generic drugs are treated the same as pioneer drugs. They are given a DIN indicating authorization to manufacture and sell the pharmaceutical.Generic products must have ongoing quality control programs to ensure consistent potency, stability, efficacy and safety of every batch of product. They must be manufactured using GMP and use approved packaging, labeling and advertising.³

Is there any difference, other than cost, in using a generic versus a pioneered product? There can be. When generic products are assessed for bioequivalence, there is a predetermined allowance for a differing concentration and absorption rate than the original product. This is insignificant for drugs with a wide therapeutic and safety margin, but it can be important for drugs with a narrow therapeutic index or for patients with compromised drug elimination pathways.⁴ In addition, human generics are evaluated for bioequivalence in humans but not animals.⁴ This may be problematic for drugs with pharmacokinetics that vary between species, especially drugs with narrow therapeutic margins.⁴ This should be emphasized to clients taking prescriptions to human pharmacists, because pharmacists sometimes make substitutions.
Compounded Drugs

Drug compounding is the mixing of two or more ingredients, of which at least one is a pharmacologically active component, to create a final product in an appropriate form for dosing an individual patient.\textsuperscript{1} Reconstituting or any other manipulation done in accordance with the directions on an approved drug’s labeling material is not compounding, but the mixing of different drugs in a clinic prior to use is compounding.

Compounding is an ancient art. More than 50\% of the medication sold by veterinarians was compounded until the 1950s when more and more manufactured drugs became available. Compounding has made a resurgence in recent years. In 2009, there were > 5000 drug compounders in the USA. By 2012, there were > 7500 drug compounders in the USA. Why so much compounding? Money! The veterinary drug market is worth billions of dollars, and veterinary drugs have been an additional source of revenue to pharmacies during tough economic times.\textsuperscript{5}

Compounded drugs are often prescribed in veterinary medicine. Drug compounding enables veterinarians to obtain drugs that are otherwise unavailable, because they have been removed from the market due to human safety concerns, pharmaceutical company mergers, or limited market size.\textsuperscript{2} Drug compounding also allows veterinarians to mix, dilute, concentrate, flavor, or even change a drug’s formulation to accommodate specific patients.\textsuperscript{1,5}

Compounded drugs are not generic drugs. Compounded drugs have no DIN, are not tested for bioequivalence, and are not produced under the guidance of GMP.\textsuperscript{1} Compounded drugs are regulated and enforced provincially but are produced in accordance with Health Canada Policy Guidelines Regarding Compounding. The guidelines are in place to ensure that patients receive safe and efficacious products, that there are no violative food residues, and that compounding doesn’t circumvent the regular process of drug application, certification, and production.\textsuperscript{1,7}

Compounding must be done by a licensed pharmacist or veterinarian.\textsuperscript{1} A compounded drug should only be produced for an animal with a valid veterinary-client-patient relationship on an as-needed basis.\textsuperscript{1,7} Compounders should only make products in limited quantities ahead of time for anticipated prescriptions with a demonstrated historical need. An animal must be suffering or its health threatened without treatment.\textsuperscript{7} Cost is not an acceptable reason for prescribing a compounded product except in extreme circumstances.\textsuperscript{1,7} There can be no equivalent veterinary or human product already available.\textsuperscript{1} The compounded drug must be safe, efficacious and within 10\% of the concentration on the label. Veterinarians should obtain written consent from owners indicating that the owner knows that a compounded drug is being used and that this specific product has not been approved for efficacy.\textsuperscript{15} No proof of consent is required for commonly used drug combinations such as, for example, ketamine and diazepam. Compounding drugs on the prohibited list for food animals is forbidden.

There are potential pitfalls when using compounded products. Reformulating a product may change its stability, potency or bioavailability. Compounders do not have to determine the bioavailability of their products. Therefore, the rate and amount of absorption may vary. Altering the formulation can change a drug significantly. For example, changing the pH of some drugs by 1 unit can change stability by a factor of 10.\textsuperscript{8} An example is omeprazole suspensions that were found to give a significantly lower serum concentration and poorer efficacy compared to the patented paste, Gastrogard\textsuperscript{9}. This was attributed to the suspensions being more acidic, and omeprazole is less stable in acidic solutions.\textsuperscript{9} Flavouring can alter the stability of a drug. Orbifloxacin was found to be 61\% of its original strength by day four when the flavouring Lixotinic was added, but it was stable when a variety of other flavourings were used.\textsuperscript{10} Addition of water causes hydrolysis of some drugs.\textsuperscript{8} Reformulating a drug into a transdermal form by combining it with a penetration enhancer is a common procedure. This is efficacious for methimazole, but many other drugs - such as morphine, dexamethasone and fluoxetine - are poorly absorbed in transdermal products.\textsuperscript{11-14} Compounders use stability studies to give an
expiration date when possible, but if there is no data available, then the compounder is required to use 25% or less of the “beyond use” date of the original product.\(^1\) In the USA, compounders may quote six months for solid products and 14 days for aqueous solutions.\(^2\)

According to Canadian compounding guidelines, a pharmacist compounds a product according to the request or prescription of the veterinarian, and **the veterinarian then takes responsibility for the safety and efficacy.**\(^1\) Pharmacists are not required to test compounded products for efficacy, bioavailability, stability or safety. If the compounded drug is being used in a performance animal, it is the veterinarian who must provide a new withdrawal time. The Global Food Animal Residue Avoidance Databank (gFERAD) does not provide withdrawal times for compounded products.

The CVMA has compounding guidelines on its website.\(^7\) These guidelines provide a scripting hierarchy. Veterinarians should choose a drug based on the least risk to both the patient and public. When possible, an approved veterinary drug with a DIN and label instructions should be used. If none is available, then an approved veterinary drug with a DIN can be used extra-label. When no veterinary drug is available, then an approved human drug with a DIN is used extra-label. When neither of these is possible, then a compounded drug that contains an approved veterinary drug is used (extra-label). If this isn’t available, then a compounded approved human drug with a DIN is used. A compounded drug containing an active pharmaceutical ingredient (as opposed to a drug with a DIN) is only used if none of the previous choices are available. The CVMA compounding guidelines have been included in some provincial veterinary association guidelines and can be used for guidance during investigations into allegations of professional misconduct in regard to the use of compounded drugs.\(^15\)

There are label requirements for compounded products. Labels should indicate that the product is compounded. There is no DIN, but there may be an alternative, compounding number. There should be a list of active ingredients; the date of compounding; names of the patient, owner, prescribing veterinarian, pharmacist or pharmacy; expiration date; dosage regime; and proper storage recommendation. See the CVMA or CVO websites for label requirements.\(^7,15\)

Here are a few steps to help ensure a good product:

8. Use the services of a qualified compounder. Don’t hesitate to ask for their compounding credentials.
9. Use a compounder located nearby.
10. Don’t use a compounder who is imitating available products.
11. Don’t buy batches of active ingredients to sell to other clinics.
12. Ask about the process that is being used to compound a product. Has it been validated for that particular product? What is the active ingredient, and where was it obtained? Is there quality assurance testing?
13. Do they analyze the end product for concentration, stability or contamination?
15. Always obtain informed consent from owners when prescribing a compounded product.
16. Document all reactions and treatment failures and report them to both the compounder and the VDD.
17. Have predetermined and practical clinical assessment parameters for efficacy and toxicity before dispensing the drug. Can you monitor the serum concentrations? Response? Adverse reactions?

We need compounded drugs, but they should be used judiciously. It is the responsibility of the pharmacist to prepare the product as per the prescription and to use good compounding practices. The veterinarian takes responsibility for the efficacy and safety, not the pharmacist. Just because something is available doesn’t mean that it is efficacious!
Pirated Drugs

Pirated drugs are medications that are manufactured and sold without having been assessed by Health Canada for bioequivalence, safety or efficacy. They have no DIN to indicate authorization for production and are not necessarily produced in accordance with GMP. Pirated drugs are mass produced from bulk active pharmaceutical ingredients (APIs) in contravention of patent and compounding laws. The APIs may be imported from a third-world country. The World Health Organization has previously estimated that up to 25% of third-world bulk APIs may be substandard or fakes.6 Companies producing patented or generic products are legally obligated to test the purity of all APIs that they use, whereas a company producing a pirated product is not. Pirated products may be sold under the guise of compounded drugs. Veterinarians should not buy bulk batches of compounded medication for resale to clients or imitations of approved products, because, by definition, these are pirated drugs.

Dispensing pirated drugs is providing substandard care. The efficacy, safety, potency and stability of these products have not been proven and may not be monitored. Practicing good-quality veterinary medicine requires prescribing safe and efficacious drugs.

References


Medicating and Monitoring the Epileptic Patient
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WHAT IS EPILEPSY?
Epilepsy is any chronic neurological condition characterized clinically by recurrent seizures. It is the most common neurological disorder in dogs. Approximately 0.5–5.7% of dogs develop epilepsy (Chandler 2006; Schwartz-Porche 1986).

HOW IS EPILEPSY CLASSIFIED?
Human epilepsy is subdivided into more than 40 syndromes by the International League Against Epilepsy (ILAE) (Engel 2001). These syndromes are differentiated by the age of onset, seizure characteristics, electroencephalographic (EEG) abnormalities, and the stimulus that induces the seizures. The syndrome determines the best treatment regimen.

We are not as exacting in veterinary medicine, because veterinarians rarely do EEGs and usually rely on owners’ descriptions of seizures. In veterinary medicine, we simply classify seizures as partial or generalized based on seizure characteristics.

Partial seizures are highly variable clinically. These seizures may consist of elementary motor events such as facial muscle or toe twitching, or more complex behaviors such as drooling, “fly catching,” excessive vocalization, or random running. Animals are conscious throughout. These seizures occur due to abnormal foci in the cerebral cortex or regions of the forebrain such as the hippocampus. The seizures reflect the area of the brain from which they arise. Partial seizures may progress over time to generalized seizures.

Generalized seizures are tonic-clonic, myoclonic or absence seizures, and animals are unconscious throughout. These seizures occur due to simultaneous activation of both cerebral hemispheres with distorted electrical activity in all or most of the brain.

WHAT CAUSES EPILEPSY?
Seizures occur following the release of electrical impulses within the brain at inappropriate times or higher-than-normal intensities. The inappropriate impulses interfere with normal nerve transmission, leading to convulsions characterized by abnormal motor or behavioral activity. There are a variety of etiologies. These include numerous genetic mutations that affect neurotransmission within the brain or hyperexcitable areas secondary to trauma, toxins, or ischemic events.

There are four seizure categories based on etiology; the first three are considered forms of epilepsy.
1. **Idiopathic epilepsy** is recurrent seizures with no identifiable underlying lesion. It occurs due to a genetic abnormality. Investigation into the mutations, patterns of disease and inheritance that cause epilepsy in companion animals is still in its infancy. Standard Poodles, Finnish Spitz, Vizla and Belgian Tervuren are known to develop familial epilepsy.
2. **Symptomatic epilepsy** is recurrent seizures due to one or more structural lesions within the brain, such as an abscess or tumor.
3. **Probable symptomatic epilepsy** (formerly cryptogenic) is recurrent seizures that are believed to be symptomatic, but the underlying lesion cannot be located.
4. **Reactive seizures** occur due to metabolic or toxic diseases. These are not considered epilepsy.
Diagnosis
The diagnostic workup for epilepsy begins with a complete history to determine the age of onset and seizure characteristics. For example, did the seizures start as partial and evolve to generalized? How long is the interictal period, and is the animal normal during this time? There should be a thorough physical and neurological examination as well as a urinalysis, complete blood profile, and serum biochemistry. If possible, do an MRI of the brain and a CSF analysis for dogs with partial seizures. Test for any local infectious diseases that are of concern.

Idiopathic epilepsy is often associated with generalized seizures and normal interictal periods. Dogs with idiopathic epilepsy usually don’t start with clustered seizures or status epilepticus. Idiopathic epilepsy typically occurs in purebred dogs that are 1–5 years of age.

Symptomatic epilepsy often starts as partial seizures that may or may not progress to generalized seizures or status epilepticus. The interictal period may be less than one month from the onset of the first seizure. Dogs that first seizure at less than one year or greater than seven years of age are more likely to have symptomatic epilepsy.

Treatment Overview
Epilepsy cannot be cured in the vast majority of dogs. The remission rate is 15% with or without therapy (Berendt et al. 2007). The mean lifespan of dogs with epilepsy is seven years with a median survival time of 2.3 years following the initial diagnosis. The survival time is not linked to whether seizures are partial or generalized (Berendt et al. 2007), but dogs with repeated status epilepticus may have a poorer prognosis.

If possible, treat the underlying disease. If the seizures are due to a space-occupying lesion, then using a glucocorticoid such as dexamethasone to decrease swelling and inflammation may be more efficacious than using an anticonvulsant.

The goal of treating epilepsy is to decrease the frequency and severity of seizures so that convulsions don’t compromise the patient’s or owner’s quality of life. This must be done cost-efficiently while avoiding adverse effects. When to start therapy? In humans, it has been shown that there is no advantage in starting therapy after a single, isolated seizure. Therefore, don’t initiate anticonvulsant therapy after a single seizure. Start therapy based on the etiology, risk of recurrence, type of seizure, and risk to patient. Begin therapy if there is a structural lesion in the brain or history of trauma; if there are two or more seizure clusters within a year, two or more isolated seizures within six months; at time of the first seizure if it occurs within a week of head trauma; if the ictal period is long (>5 minutes) or if the postictal period is prolonged or unusual. Epilepsy may progress more quickly in animals in which treatment is delayed or when subtherapeutic dosages are used (Dewey 2006).

In human medicine, the anticonvulsant is chosen based on the epilepsy syndrome (age of onset, characteristics of seizure activity, EEG pattern...). We do not have an extensive classification system or many anticonvulsants to choose from in veterinary medicine. Veterinarians typically choose the initial anticonvulsant based on familiarity, efficacy, adverse effects, cost, and owner lifestyle. Seizure type is just starting to play a role in our choice of anticonvulsant.

Start with monotherapy rather than with two anticonvulsants. There are fewer adverse drug reactions and no drug interactions to worry about; it is also less expensive and easier for owners. The most common first-line anticonvulsant for dogs is phenobarbital followed by potassium bromide (KBr). The use of newer anticonvulsants is becoming more common, but they are more costly and often require more frequent therapy because of shorter half-lives. If an animal doesn’t tolerate a particular anticonvulsant, then an alternative anticonvulsant is tried. If monotherapy cannot control the seizure activity adequately at safe doses, then add a second or even third anticonvulsant to the treatment regime.
Treatment failure is common. It can occur due to an incorrect diagnosis; the nature or progression of the underlying abnormality; because an anticonvulsant is ineffective in a particular animal; insufficient anticonvulsant dosage; or because an animal develops an adverse reaction to an anticonvulsant at a lower dose than that which can control the seizures. In humans, 47% of individuals respond to the first antiepileptic drug, 13% respond to a second, and 3% respond to a third.

**Phenobarbital**
Phenobarbital is the most common first-choice anticonvulsant for dogs. It is an effective monotherapy in > 70% of animals. The mechanism of action is via an increase of the inhibitory effects of GABA within the brain, anti-glutamate effects and a decreased Ca++ influx into neurons. Phenobarbital is metabolized by cytochrome (CYP) P450 enzymes in the liver. It also induces increased production of these enzymes, subsequently increasing the rate of its own metabolism and that of other drugs that are metabolized by CYP enzymes.

The half-life of phenobarbital in dogs is highly variable and can range from 15 to more than 100 hours (Levitski, Trepanier 2000). Phenobarbital can cause several adverse effects including sedation, ataxia, polyphagia, polyuria, polydipsia, and behavioral changes. Most dogs will exhibit some of these effects during the first few weeks of therapy, but they usually spontaneously resolve within the first month. Rare cases of reversible blood dyscrasias and irreversible idiosyncratic superficial necrotizing dermatitis have been reported. Phenobarbital can increase serum triglycerides and predisposes dogs to pancreatitis (14% incidence was reported in dogs on phenobarbital monotherapy versus 42% in dogs receiving a combination of phenobarbital and KBr) (Kluger et al. 2008; Bizzeti et al. 2006).

Phenobarbital can cause a dose-related hepatotoxicity that is more likely to occur in an animal whose serum concentration is at the upper end of or above the therapeutic range. However, some animals develop hepatotoxicity at lower concentrations. The hepatotoxicity may be reversible if it is detected early. Do not use phenobarbital in a dog with preexisting liver disease, because it is both metabolized in the liver and is potentially hepatotoxic.

Animals are started at the lowest possible daily dosage of phenobarbital that achieves a serum concentration within the therapeutic range. Some references suggest starting at 1–2 mg/kg. Most dogs started at 1 mg/kg of phenobarbital will have a steady-state concentration well below the therapeutic range (54–190 µmol/L). Starting at 2.5 mg/kg is more likely to result in a concentration within the target range. If seizures are sufficiently controlled, then continue with that dosage. If seizure activity is still unacceptable, then increase the dosage as required, monitoring the serum concentration to ensure that the levels don’t exceed the therapeutic range. It is best to maintain a dog within the desired range and keep seizures to less than one per month if possible. Some animals may start to exhibit dose-related toxicities, and the possibility of hepatotoxicity increases at the upper end of the therapeutic range. Most dogs are treated with 4–16 mg/kg/day of phenobarbital divided BID. A loading dose of 6–12 mg/kg can be used if required clinically. If intolerable side effects persist after the first month of therapy, then the therapy should be changed to an alternative anticonvulsant.

Most dogs are treated BID with phenobarbital. If you are having difficulty with seizure control, it could be that the animal metabolizes phenobarbital more quickly than most animals. If the half-life is less than 30 hours, then treat the animal TID. The half-life can be calculated by measuring the peak and trough concentrations.

When should you add a second anticonvulsant? If the seizure control is insufficient with phenobarbital, then you may want to consider the addition of a second anticonvulsant once the serum concentration is > 120 µmol/L. There is still room in the range for increasing the phenobarbital dosage, and some owners may prefer to stay with monotherapy as long as possible; but this is when you should start to discuss the likelihood of requiring a second anticonvulsant at some time in the future. The most
common second anticonvulsant is still KBr, but newer drugs such as levetiracetam, zonisamide or gabapentin are being used more and more. Potassium bromide typically causes a 50% reduction in seizure frequency when used with phenobarbital. If a dog is receiving both phenobarbital and KBr, and there is no seizure activity for 6 months, then you may be able to decrease the phenobarbital dosage. This is not possible in all dogs. Weaning should be done gradually in small increments every 6 weeks.

**Potassium Bromide**

Potassium bromide is the oldest human anticonvulsant. It is believed to hyperpolarize neurons by competing with Cl⁻. The half-life of potassium bromide (KBr) is 24 days, and it takes 3–4 months to reach steady state. The most common adverse effects of KBr are gastric irritation, polyuria, polydipsia, polyphagia with weight gain, pelvic-limb stiffness or weakness, sedation, ataxia, and behavioral changes. A potentially lethal pancreatitis can occur when using a combination of phenobarbital and KBr (Gaskill, Crib 2000). Aggression has been reported. KBr is excreted unchanged by the kidneys and therefore, unlike phenobarbital, it can be given to dogs with hepatoopathies. Diets high in salt can lower the serum concentrations of KBr, because Br⁻ competes with Cl⁻ for reabsorption in renal tubular cells.

KBr is usually started at 15 mg/kg BID or 30 mg/kg SID. It takes a few weeks for the full clinical effect to occur and 3–4 months to reach steady state because of the long half-life. The typical maintenance dose is 10–30 mg/kg BID. If there is severe seizure activity and you require a full clinical effect more quickly, then you can use a loading dose. The loading dose is 450 mg/kg divided into equal doses over five days added to the maintenance dose of 30 mg/kg (120 mg/kg/day for 5 days, divided BID to minimize GI irritation). A loading dose gives an immediate clinical effect and steady state, but you are more likely to cause adverse effects such as gastrointestinal irritation or sedation. Following a loading dose, the serum KBr should be measured at one week and 2–3 months. The therapeutic range of KBr is ~12.5–31 mmol/L when used with phenobarbital or up to 40 mmol/L if used as a monotherapy. Bromide is available as either KBr or NaBr. Decrease the dose by 15% if NaBr is used.

**Should I Start with Potassium Bromide or Phenobarbital?**

Phenobarbital is still the most commonly used anticonvulsant for monotherapy in dogs. A study published in 2012 compared 21 epileptic dogs receiving phenobarbital monotherapy to 25 epileptic dogs receiving KBr monotherapy (Boothe et al. 2012). The researchers found that 85% of dogs receiving phenobarbital monotherapy responded compared to 52% of dogs receiving KBr monotherapy. The seizure activity worsened in low numbers of dogs receiving KBr. Polyuria, polydipsia, lethargy and ataxia were more common with phenobarbital. Vomiting was more common with KBr. The vomiting due to KBr persisted for more than a month in some dogs; however, this may have been due to the particular formulation of KBr that was used (Boothe et al. 2012).

Therefore, phenobarbital is efficacious in more dogs than KBr, and its shorter half-life makes it easier to make changes in the serum concentration. The major drawback to using phenobarbital is that there are more adverse reactions than with KBr, including a potentially fatal hepatotoxicity. Poorer efficacy and a long half-life are the main drawbacks to using KBr. A loading dose can be used for KBr to enable it to reach its full clinical effect quickly, but this may cause vomiting.

**Monitoring of Dogs Receiving Phenobarbital and Potassium Bromide**

Serum biochemistries should be done every 6–12 months in dogs and cats receiving anticonvulsants. For dogs being treated with phenobarbital, liver enzymes should be closely monitored because of possible hepatotoxicity. Phenobarbital induces increased production of canine ALP within three weeks of initiating therapy. Therefore, it is normal for ALP to be elevated in dogs receiving phenobarbital. This induction varies between animals. We have measured greater than 2000 IU ALP in otherwise healthy dogs receiving phenobarbital. It is also normal for ALT to be mildly increased due to induction. If the ALT
is greater than three times the upper end of the normal reference interval, then consider possible phenobarbital hepatotoxicity and do additional diagnostic testing to test the liver function, such as pre- and postprandial bile acids and abdominal radiography or ultrasound. Dogs with evidence of liver disease should be immediately changed to an alternative anticonvulsant that is not metabolized in the liver and is not associated with hepatotoxicity, such as KBr or levetiracetam.

Therapeutic drug monitoring (TDM) is the measurement of the plasma or serum drug concentration in your patient to determine if the dosage is correct. It should be done when a drug reaches its steady-state concentration after initiating therapy or changing the dosage and every 6–12 months thereafter. This means waiting 10–14 days after a change in a phenobarbital dose and 3–4 months after a change in a KBr dose. If a loading dose of KBr has been used, then measure the KBr at one week and 3 months following the loading dose.

When should you sample animals for TDM? There is a significant difference between concentrations at trough and non-trough times (especially in animals at higher concentrations), and it is best to be consistent to allow better comparison between samples (Monteiro et al. 2008). If you are concerned about phenobarbital toxicity, then do a peak sample at 4–8 hours posttreatment. For regular therapeutic drug monitoring, trough samples taken just before the next treatment are best. If the response to treatment is poor and you are suspicious that the phenobarbital half-life may be short, then take both a peak and trough sample from these animals. This enables the calculation of the half-life of phenobarbital for that individual. Avoid serum separator tubes for serum samples when measuring phenobarbital, because silicone binds to phenobarbital.

**What If Phenobarbital and/or KBr Don’t Work?**

Dogs that cannot be controlled with adequate serum concentrations of phenobarbital and KBr, or dogs that have toxicities at subtherapeutic dosages of phenobarbital and KBr have “refractory” or “intractable epilepsy” (Platt et al. 2006). Approximately 30% of canine epilepsy eventually becomes refractory. These animals require a third anticonvulsant. The third-line antiepileptic drugs tend to be newer human epilepsy products for which the pharmacokinetics, efficacy and safety is known for dogs and cats. No add-on anticonvulsant is efficacious in all animals.

**Levetiracetam (Keppra®)**

Levetiracetam is used as either an add-on or monotherapy in humans with partial seizures. Levetiracetam binds to an integral protein called synaptic vesicle protein 2A that then modifies the release of neurotransmitters. Levetiracetam also has neuroprotective properties and may actually improve some pathological changes in the brain.

In dogs, levetiracetam is 100% bioavailable with a half-life of 3–4 hours and a clinical effect within 24 hours. The majority is excreted unchanged in urine. It is considered a safe drug with minimal adverse effects, but it can cause ataxia, sedation and vomiting. It does not cause hepatotoxicity.

To avoid sedation, start treatment gradually with 20 mg/kg BID and then increase to 20 mg/kg TID. Continue to increase in 20 mg/kg increments to effect, unless unacceptable side effects occur. Studies suggest that 60% of dogs respond initially; however, after 4–8 months, there is a loss of effect in 2/3 of previous responders due to tolerance (Volk et al. 2008). Therefore, it is said to have a honeymoon period in many dogs.

Levetiracetam has a wide therapeutic margin. It is not yet standard to do therapeutic monitoring, but having a baseline concentration may be of value in establishing an individual’s pharmacokinetic pattern. A therapeutic range for dogs has recently become available.
Zonisamide (Zonegran®)
Zonisamide is a human anticonvulsant for partial and generalized seizures that works by blocking voltage-dependent Na⁺ and Ca²⁺ channels. It may also reduce presynaptic glutamate release and decrease dopamine and serotonin effects in parts of the brain.

Zonisamide is well absorbed in dogs (including rectally) and has a half-life of 15–20 hours. It has low protein binding. Some is metabolized by P450 enzymes, but much is excreted unchanged in the urine. The adverse effects are usually mild, such as transient ataxia, lethargy and vomiting, but zonisamide is a sulphonamide-based drug and can cause keratoconjunctivitis sicca and metabolic acidosis. A non-fatal hepatopathy in a dog has been attributed to zonisamide.

Zonisamide can be used as an add-on or monotherapy in dogs. A study in Europe using 10 mg/kg BID showed a response in 80% of dogs with refractory epilepsy. The seizure activity decreased overall by 82% (von Klopmann et al. 2007). Other studies have demonstrated more conservative results, with a decrease in seizure frequency in 50% of refractory cases.

Zonisamide treatment is started at 5 mg/kg BID. The dosage may need to be increased if it is used in combination with phenobarbital due to enhanced metabolism by P450 enzymes. Like levetiracetam, some dogs have a honeymoon period and stop responding after 3 months due to the development of tolerance (von Klopmann et al. 2007).

Gabapentin (Neurontin®)
Gabapentin is a structural analogue of GABA that enhances the release and action of GABA while also inhibiting Na⁺ and Ca²⁺ ion channels. Gabapentin is absorbed from the duodenum by a saturable transport system. Therefore, the bioavailability decreases as dosages get higher. The slow-release tablet is not advised, as it is poorly absorbed due to saturation. Approximately 60–70% is metabolized to N-methyl-gabapentin in the liver, and the rest is excreted unchanged in the urine. The half-life of gabapentin in dogs is 3–4 hours, and therefore treatment must be TID or QID. Possible adverse effects include mild sedation, polyphagia and pelvic-limb ataxia.

Gabapentin has a variable effect. In one study of 17 dogs with refractory seizures, there was no change in the overall seizure activity, but there was an increase in the average interictal period. Three dogs stopped having seizures entirely, but there was no effect in 40–50% of dogs (Govendir et al. 2005).

Gabapentin is started at 10 mg/kg TID. Studies have safely used 25–60 mg/kg divided TID–QID (Dewey 2006). There have been no long-term trials, but it appears to be well tolerated.

Pregabalin (Lyrica®)
Pregabalin is a structural analogue to gabapentin but has a longer half-life in dogs than gabapentin (7 hours versus 4 hours). In one small trial, 7 of 9 dogs responded to pregabalin as an add-on, with a 50% decrease in seizures in animals refractory to phenobarbital, KBr or a combination of the two (Dewey 2009). All dogs in the study experienced some sedation and ataxia. It can also cause hind-limb ataxia in dogs.

Felbamate (Felbatol®)
Felbamate acts on GABA and NMDA receptors. It was approved for partial and generalized seizures in people in the 1990s, but subsequent deaths in people due to idiosyncratic aplastic anemia or liver failure resulted in it being withdrawn from the market in Canada. It is still available in the USA.

Felbamate is considered safe in dogs. Mild hepatotoxicity, reversible blood dyscrasias and keratoconjunctivitis sicca (KCS) have been reported. Felbamate does not cause sedation. The half-life in dogs is 5–6 hours. It has been used as both a third-line anticonvulsant and as monotherapy in dogs. Start treatment at 15 mg/kg TID and increase in increments of 15 mg/kg TID every two weeks as required to control seizures (Dewey 2006). Avoid felbamate in dogs with hepatic disease.
Sixty percent of dogs respond to felbamate. This drug may be a good choice in dogs with symptomatic epilepsy and decreased mentation, as it doesn’t cause sedation.

**Feline Epilepsy**

Most feline epilepsy is symptomatic. Idiopathic epilepsy is less common in cats than in dogs because of a larger genetic pool. Therefore, unlike canine epilepsy, feline epilepsy is usually characterized by partial seizures. However, 90% of seizuring cats will experience generalization of partial seizures on at least one occasion (Volk et al. 2007). The partial seizures may consist of simple movements such as facial twitching, rhythmic limb or head jerking, or complex movements such as running bouts or vocalization. Cats can also develop behavioral seizures that can have the appearance of unwarranted aggression with hissing, growling, piloerection or can be suggestive of panic or a compulsive behavior.

Phenobarbital is the most commonly used anticonvulsant for feline epilepsy. It completely eliminates seizures in 45% of cats and adequately controls seizure activity in a further 30%. Seizures reappear or are not controlled from the start in 25% of cases (Volk et al. 2007). The phenobarbital pharmacokinetics in cats is less variable than in dogs. The half-life in cats is 34–43 hours. Cats do not develop tolerance to phenobarbital.

Phenobarbital causes dose-related adverse reactions in cats such as polyuria, polydipsia, polyphagia, sedation and ataxia and can cause idiosyncratic effects such as blood dyscrasias, dermatitis, and persistent unusual behaviour. Cats are more sensitive to the sedative effects than dogs but do not develop phenobarbital-induced hepatotoxicity.

Start cats with 1–2 mg/kg of phenobarbital once daily. Cats are only treated BID if necessary. Alternatively, start with 7.5 mg initially and increase in increments of 7.5 mg.

KBr should not be used in cats. It is efficacious but can cause an asthma-like respiratory syndrome in >70% of cats.

Cats that are refractory to phenobarbital can be given a second anticonvulsant as an add-on. This has traditionally been a benzodiazepine (diazepam or clonazepam). Unlike dogs, cats do not develop tolerance to diazepam. The diazepam dosage is 0.5–2 mg/kg divided BID or TID. It is best to increase the dosage gradually to avoid excessive sedation. A major drawback to using diazepam in cats is that it can cause an idiosyncratic fulminant hepatic necrosis. Clonazepam has become more popular, because it is less likely to cause hepatitis in cats. Because there are now safer options, diazepam is being used less commonly as an add-on anticonvulsant in cats. Dewey of Cornell advocates levetiracetam as the second-line AED for cats. The half-life of levetiracetam in cats is 3 hours. In one study, 20 mg/kg TID resulted in an overall decrease in seizure frequency of 60% in 7 of 10 cats (Dewey 2006). Levetiracetam causes a dose-related lethargy and anorexia in cats.

Gabapentin has been used in cats. Start with 5–10 mg/kg SID and then go to BID or TID as required (Dewey 2006).

There is insufficient information concerning the efficacy of zonisamide in cats; however, it is known to cause mild ataxia, anorexia and somnolence.

**References**

Adverse Drug Reactions
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The World Health Organization defines an adverse drug reaction (ADR) as a “noxious or unintended response to a drug that occurs at an appropriate dose used for prophylaxis, diagnosis, or therapy.”¹

Adverse drug reactions are common. Approximately 6.5% of all admissions to human hospitals in the western world are due to an ADR.²,³ Adverse drug reactions are one of the leading causes of human deaths in the USA.³ We don’t know the number of ADRs in veterinary medicine, but if you practice veterinary medicine and prescribe drugs, then you will prescribe medication that causes an ADR in a patient. An ADR may be merely a minor side effect and accepted annoyance of taking a particular drug, or it may be a severe, life-threatening reaction.

Adverse drug reactions can be classified mechanistically as either dose-dependent or dose-independent (idiosyncratic).⁴ Dose-dependent ADRs can be either pharmacological toxicities or intrinsic toxicities.

A) DOSE-DEPENDENT ADVERSE DRUG REACTIONS
The majority (> 75%) of ADRs are dose-dependent, predictable reactions; the higher the dose or longer the duration of therapy, the greater the number of patients affected and more severe the ADR.²,⁴ Dose-dependent ADRs are detected by pharmaceutical companies during clinical trials before a product is approved for sale. They can be reproduced experimentally. These reactions are often avoidable by careful dosing and monitoring of the patient.

Hypersusceptible animals develop a dose-dependent ADR or side effect at a lower therapeutic dosage than in most animals. This may be because of an individual hypersensitivity due to a genetic polymorphism (these genetic polymorphisms are typically variants of a gene for an enzyme or receptor that is involved in the processing or action of a drug) or alternatively because the serum concentration of a drug is elevated due to altered drug pharmacokinetics in an animal (pharmacokinetics describes drug absorption, distribution, metabolism and excretion from the body). Label dosages are based on an
animal having expected pharmacokinetics for that drug. Altered pharmacokinetics can occur due to age (neonatal or geriatric), pregnancy, concurrent diseases, or drug interactions.

The best known genetic polymorphism that predisposes to dose-related ADRs is the mutation in the ABCB1 gene (MDR1). This gene codes for p-glycoprotein, a multidrug transporter located in the blood-brain barrier, intestinal wall and kidneys. Collies and some other herding breeds have an increased prevalence of heterozygotes or homozygotes for this mutation. Affected animals have decreased or no p-glycoproteins. As a result, these animals are hypersusceptible to neurotoxicity from drugs that are usually effluxed from the brain by p-glycoprotein, because increased amounts of the drugs are allowed past the blood-brain barrier. This includes the drugs ivermectin, vincristine, loperamide and acepromazine. These drugs can cause neurotoxicity in all animals if they are given sufficiently high doses, but animals with a mutation in the ABCB1 gene develop the neurotoxicity at low dosages.

There are also other, lesser-known genetic polymorphisms that alter the pharmacokinetics of drugs. Greyhounds also have lower concentrations of some types of cytochrome P450 enzymes. This polymorphism affects the metabolism of thiopental and contributes to the slow recovery of Greyhounds from this drug.

Neonates tend to have a higher body-water content and therefore a higher volume of distribution, which can lead to a lower initial serum concentration of some drugs. Neonates can also have a lower clearance rate and immature metabolizing enzyme systems, which may prolong the half-life of other drugs. Neonates also have less fat than older animals, and, therefore, the dosage of fat-soluble drugs may need to be decreased.

The glomerular filtration rate decreases in geriatric patients, which can decrease the clearance of some drugs. This can be problematic for drugs with narrow therapeutic margins that are renally excreted. For example, older cats with compromised renal function are more likely to develop renal toxicity secondary to enrofloxacin, because it isn’t excreted as quickly and therefore may reach a higher serum concentration.

Concurrent diseases that can affect the pharmacokinetics of drugs include gastrointestinal, renal and hepatic disease. In general, it must be a severe disease to have a significant effect on the pharmacokinetics of a drug. Gastrointestinal disease can alter the absorption of a drug. Renal disease can decrease the clearance of any drugs that are cleared through the kidneys. Renal disease increases the nephrotoxic potential of drugs such as aminoglycosides. Renal disease can also lead to a decrease in the serum protein concentration, which then increases the potential toxicity of highly protein-bound drugs such as nonsteroidal antiinflammatory drugs (NSAIDs). Hepatic diseases can affect the metabolism of drugs that are normally metabolized or cleared in the liver, such as propranolol, benzodiazepines and phenobarbital. The liver has to be > 80% compromised before there is a clinically significant effect on the drug pharmacokinetics.

Drug interactions may also change the pharmacokinetics of a drug sufficiently to cause an adverse reaction. Phenobarbital induces the production of cytochrome P450 enzymes, and therefore any drug that is metabolized by these enzymes is metabolized and excreted more quickly in patients that are being treated with phenobarbital. In contrast, chloramphenicol inhibits the production of some cytochrome P450 enzymes, and therefore it can decrease the metabolism and prolong the half-life of drugs that are metabolized by P450 enzymes, such as phenobarbital or cyclophosphamide. Enrofloxacin and cimetidine both increase the possibility of theophylline toxicity because of either inhibiting the clearance (enrofloxacin) or the metabolism (cimetidine) of theophylline. Ketoconazole and cyclosporine inhibit the multidrug transporter p-glycoprotein. Therefore, drugs that are normally pumped away from the brain by p-glycoprotein may be able to cross the blood-brain barrier if an animal is receiving
ketoconazole or cyclosporine. Drugs that affect the acidity of the stomach may alter the absorption rate of drugs given concurrently.

Drug interactions can also affect the pharmacodynamics (the effects) of a drug. For example, glucocorticoids and NSAIDs taken together increase the potential for gastrointestinal toxicity, and opioids given with general anesthetics have an increased potential for respiratory depression.

1) Dose-Dependent Pharmacological-Based Adverse Drug Reactions
Pharmacological-based dose-dependent ADRs are undesired pharmacologic effects of drugs acting on specific targets or receptors. This can be an exaggerated primary response, such as a drug that is used to lower blood pressure causing hypotension. Alternatively, it can be unavoidable secondary effects, such as those of NSAIDs. NSAIDs work by inhibiting prostaglandin production. Therefore, they can cause unwanted side effects by inhibiting the production of prostaglandins that are normally protective.

These ADRs are treated by discontinuing the drug, providing supportive therapy as required, and determining if the reaction occurred because the animal had altered pharmacokinetics, genetic susceptibility, or it was due to an error in the dosage. Drugs that have caused this type of reaction can be reintroduced at a later time at a lower dosage.

2) Dose-Dependent Intrinsic-Based Adverse Drug Reactions
Intrinsic-based dose-dependent ADRs occur due to the chemical properties of a drug or its metabolites. These reactions may involve oxidative damage to cells or nonspecific binding to proteins, nucleic acids or cell membranes. The damage is usually related to the accumulation of reactive drug metabolites. Therefore, affected tissues are often at or nearby the site of detoxification. Drug metabolites may accumulate following an overdose or in an individual or species that is deficient in detoxification enzymes. The liver is a frequent site of this type of reaction, because it is the organ where most drug biotransformation (metabolism) occurs. An example is hepatotoxicity in dogs due to acetaminophen. Acetaminophen metabolism occurs in the liver. A small percentage of acetaminophen is oxidized by cytochrome P450 enzymes to a reactive metabolite. This metabolite is usually short-lived; however, if a dog is incapable of detoxifying the metabolite, then the reactive intermediate accumulates and starts to bind to nearby proteins within hepatocytes. This eventually leads to hepatocellular death and organ dysfunction.

The clinical signs of a chemical-based adverse reaction reflect the affected organ. Treatment consists of discontinuing the drug, supportive therapy, and enhancing the cell’s protective mechanisms with products such as antioxidants. Like all dose-dependent reactions, the drug can be reintroduced at a later time at a lower dose.

B) DOSE-INDEPENDENT (IDIOSYNCRATIC) ADVERSE DRUG REACTIONS
Idiosyncratic ADRs are less common (< 25% of all ADRs). These are dose-independent, unpredictable reactions that can occur at concentrations well within the usual dosing range. These are different ADRs than the predictable dose-dependent ADRs. The main distinguishing factor for this group of ADRs is that predisposed animals can develop the reaction to a particular drug at any dosage, whereas a nonsusceptible animal will not develop an idiosyncratic ADR for that drug at any dosage (no matter how high you go). Animals susceptible to idiosyncratic ADRs usually have genetic polymorphisms that predispose them to the reaction. Idiosyncratic ADRs may occur more frequently in a particular population with a common genetic polymorphism. These ADRs may not be identified until a drug has been released onto the market and administered to millions of patients. Idiosyncratic ADRs cannot be reproduced experimentally, because they are so highly dependent on individual characteristics.

Most idiosyncratic ADRs are immune-mediated reactions to drug-modified proteins or autoantigens. The reaction can be a classic rapid-onset anaphylaxis or allergy with a history of a previous
exposure, or a delayed reaction with no history of a previous exposure. For example, sulfonamides can cause a dose-independent ADR in dogs that is a delayed immune-mediated reaction 7–14 days after the initial therapy. If an animal has received a drug for 3–4 weeks with no idiosyncratic reaction, then one is unlikely to occur. The clinical presentation varies with the target tissue of the immune-mediated reaction. The reaction may be characterized by a fever, lymphadenopathy, dermatopathy, hepatopathy, nephropathy, immune-mediated hemolytic anemia or thrombocytopenia.

Treatment consists of supportive therapy and may include corticosteroids. The drug or related product that has caused an idiosyncratic reaction in an animal should never be used in that individual again, because even at a lower dose, the ADR will recur.

**Diagnosis of an Adverse Drug Reaction**

1. What are the possible explanations for the clinical signs? Do a full workup to develop a list of differential diagnoses.
2. Is the animal receiving any drug? Even animals that have been receiving a drug for years with no adverse effects can suddenly develop an ADR to a product if the pharmacokinetics change for that product or a mistake is made in the dosage.
3. Are there predisposing factors in the patient, such as concurrent medication, breed or a clinical condition? Many ADRs occur in animals with altered pharmacokinetics. Concurrent diseases that affect drug pharmacokinetics most often are gastrointestinal, renal and hepatic disease. Confirm with the owner that the animal isn’t receiving any other drugs or natural products.
4. Has the suspected ADR been previously reported? Most ADRs are dose-dependent and described on the drug label or have been reported in the literature. Dose-independent idiosyncratic ADRs are also likely to be on the labels of older products but may not be described yet for newly released medications. Consider contacting the manufacturer to inquire if similar episodes have been reported.
5. Is the temporal association of the event appropriate for the ADR that you suspect? Dose-dependent reactions usually occur while the animal is receiving the drug. Idiosyncratic ADRs usually occur within the first month of treatment and may occur up to 1–2 weeks after completion of therapy.
6. Has the drug been administered previously to the patient, and what was the outcome?
7. Do the clinical signs disappear with drug withdrawal and recur with re-exposure? This is the ultimate confirmation of an ADR, but it is often not ethical or safe to re-expose an animal.
8. Is there evidence of a dosing error or elevated plasma concentration? Ensure that there was no error on the prescription or with owner compliance. Confirm the dose and strength with the pharmacy if the prescription was filled elsewhere, and ensure that there was no substitution made with another product. If possible, measure the serum concentration of the drug. This will detect an unexpectedly high concentration, and you will know to focus your investigations on altered pharmacokinetics or an unacceptable high dose.

**Can Adverse Drug Reactions Be Prevented?**

Most ADRs are dose-dependent and therefore can be prevented or at least minimized with careful dosing that takes into consideration the individual patient. Dose-independent, idiosyncratic ADRs are more difficult to avoid, as they occur unexpectedly in animals that are genetically predisposed. However, the genetic predisposition may be higher in some populations.

Here are a few things to think about:

1. Does the animal truly require medication? Only prescribe drugs that are truly required.
2. Consider the safety and efficacy of that product. Consult the label. What are the ADRs in the
general population? If it is a human product, the ADR may not be described for your species of
interest. Review the literature; have any studies been done? Have any ADRs been reported? Does
the potential benefit of treatment warrant the potential risk?
3. Does your patient have altered pharmacokinetics due to age (neonate or geriatric), pregnancy, or
gastrointestinal, hepatic or renal disease? If so, you may need to adjust the dosage.
4. Is the patient already receiving another medication? If so, is it listed on the drug insert or in the
veterinary literature as interacting with the drug that you are considering? If there is a potential
for interaction, how will it affect the serum concentrations? Do you need to adjust the dose or
change to a different product?
5. Be aware of any breed-associated ADR. For example, 70% of Collies, 50% of Australian Shepherds
and 15% of Shetland Sheepdogs are affected by the ABCB1 mutation. Therefore, large numbers of
these animals are hypersusceptible to ADRs to any drugs that are normally pumped out of cells by
this transporter. There is a test available to determine if these animals are affected.
6. When possible, start with the lowest possible dose. Recheck the dose before you prescribe a drug
using more than one source if it is a drug that is new to you. The accepted dose of some products
can change over time, and you should be aware of trends.
7. Explain the risk and clinical signs of ADRs to the owner.
8. Know in advance how you will monitor for an ADR. This may be by discussions with owners,
rechecks, complete blood profiles, serum biochemistries or therapeutic drug monitoring.

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Antimicrobial Therapy of Bovine Respiratory Disease (BRD)

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In global terms, BRD treatment and metaphylaxis represents the most lucrative market for the veterinary pharmaceutical industry. The Holy Grail is the development of antimicrobials that require a single administration that provides an extended duration of activity. But how does plasma drug concentration relate to clinical outcome? How long should we wait to re-treat animals that appear to be non-responders? Also, is there a risk that these long acting drugs will encourage development of antimicrobial resistance? In this session we will address these questions and dispel 5 antimicrobial treatment myths relating to combination therapy, route of drug administration, class switching and using body temperature as a basis for treatment.

FIVE ANTIMICROBIAL TREATMENT MYTHS

1. Two antimicrobials work twice as well as one.
2. You must give something IV at the same time as a long-acting antibiotic to get a quick response.
3. If calves with BRD haven’t responded to the first drug, switch to another drug class.
4. Aggressive is good. If they don’t look better in 24 hours, add another drug to the treatment rotation.
5. The hotter they are, the sicker they are. Therefore, base your drug choices for respiratory disease on rectal temperatures.

“MYTHBUSTERS”

Myth 1: Two Antimicrobials Work Twice as Well as One

The Fractional Inhibitory Concentration (FIC) is one way to look at antimicrobial “synergy”. The FIC is defined in the following equation:

\[
\text{FIC} = \frac{\text{MIC of drug A} + B}{\text{MIC of drug A alone}} + \frac{\text{MIC of drug B} + A}{\text{MIC of drug B alone}}
\]

The FIC is interpreted using the criteria detailed in Table 1.

<table>
<thead>
<tr>
<th>FIC</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>&lt; 0.5</td>
<td>Synergism</td>
</tr>
<tr>
<td>0.5 to 1.5</td>
<td>Additive</td>
</tr>
<tr>
<td>2.0</td>
<td>Indifferent</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>Antagonistic</td>
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</table>
Synergistic Combinations
If we consider synergism using the FIC criteria there are very few antimicrobial combinations in veterinary medicine that are truly synergistic. In some cases, synergism may be pathogen specific and cannot be universally applied across all species or all isolates. Some examples of drug combinations that demonstrate synergism are:

- Combination of a beta-lactam with sulbactam or potassium clavulanate
- Combination of a sulfa with a diaminopyrimidine (potentiated sulfa)
- Aminoglycosides and beta-lactams (some combinations)

Antagonism Examples
In some cases, the veterinary tendency towards polypharmacy and the belief that “more is better” may in actual fact be harmful to our patients. One such example is the combination of chlortetracycline (bacteriostatic protein synthesis inhibitor) and penicillin (bacteriocidal cell wall synthesis inhibitor). Penicillin requires actively dividing bacteria that are producing cell walls to exert a bacteriocidal (killing) effect. Chlortetracycline reversibly binds to the 30S ribosomal subunit thereby inhibiting bacterial multiplication. Chlortetracycline therefore inhibits optimal penicillin activity.

This antagonism has been demonstrated in controlled clinical trials in humans with pneumococcal meningitis. In one study, children with meningitis responded better to ampicillin alone than a combination of ampicillin, chloramphenicol and streptomycin.

Burrows and Ewing (1989) demonstrated mixed synergism, additive effects and indifference for combinations of erythromycin and oxytetracycline or spectinomycin against Pasteurella (Mannheimia) haemolytica (Journal of Diagnostic Investigation. 1989;1:299–304). For example, the combination of erythromycin and spectinomycin was found to be synergistic, additive and indifferent against 15, 13 and 6 isolates respectively. Ose and others demonstrated in-vitro synergism between tylosin and oxytetracycline against Pasteurella (Mannheimia) haemolytica but the clinical relevance of this is not known (VM SAC Veterinary Medicine and Small Animal Clinician 1976;71:92–95).

Take Home Message
Synergism between antimicrobials is extremely variable. There is also a high possibility of antagonism between some combinations, such as β-lactams with bacteriostatic agents like oxytetracycline and the macrolides.

The main body of clinical “evidence” for combination antimicrobial therapy is anecdotal. We suggest saving the money and the needle hole by relying on one antimicrobial at a time for BRD.

Myth 2: You Must Give Something IV at the Same Time as a Long-Acting Antibiotic to Get a Quick Response
Table 2.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Serum or plasma Tmax reported range or mean ± SD (hours)</th>
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<tr>
<td>Ampicillin trihydrate - 7.7 mg/kg IM</td>
<td>1.1 ± 0.63</td>
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</tbody>
</table>
Table 2 illustrated that many of the BRD therapies considered “long acting” achieve peak plasma drug concentrations in < 1 hour. The exceptions would be oxytetracycline, florfenicol and procaine penicillin. Therefore in many cases, our desire to give something IV is more to placate the producer who expects us to “do something” rather than actually having a scientific reason for doing something.

Myth 3 and 4: When Should We Switch Drugs; The Concept of Post-Treatment Intervals

The following list contains examples of single injection (Long Acting) BRD antimicrobials:
- Enrofloxacin (Baytril 100®, Bayer)
- Florfenicol (Nuflor®, Schering-Plough)
- Tilmicosin (Micotil®, Elanco)
- Tulathromycin (Draxxin®, Pfizer)
- Oxytetracycline 200 mg/ml (Liquamycin LA-200®, Pfizer, and generics)
- Oxytetracycline 300 mg/ml (Tetradure 300, Merial)

These antimicrobials are typically administered q24 or q48H:
- Ceftiofur hydrochloride (Excenel® RTU, Pfizer)
- Danofloxacin (A-180®, Pfizer)

The Million Dollar Question

Do we know enough about pharmacodynamics to predict when therapy has “expired”?
Figure 1 depicts the “ideal” treatment response. Here pathogen load increases above a certain “disease detection threshold” (horizontal line) at which time therapy is instituted. The figure depicts 2 proposed antimicrobial drug pharmacokinetic profiles. The dash line would be the anticipated plasma drug concentrations obtained with a “short acting” formulation and the solid line depicts the plasma drug concentrations obtained with a “long acting” formulation. Our “mental model” is that peak plasma drug concentrations will coincide with a reduction in pathogen load to below the disease detection threshold over time.

There are several important considerations that should be factored in to our mental model. Firstly, we do not know how pathogen load relates to disease detection. The disease detection threshold is also not a constant. It depends largely on the stockmanship, management and husbandry of the producer. Now let’s consider the scenario of bacteriological relapse:
In this scenario pathogen load initially decreases below the limit of detection but subsequently increases again to above the threshold. Clinically we would consider this to be a relapse.

Figure 2.

Figure 3 depicts the scenario likely to be encountered when an animal demonstrates bacteriological treatment failure with subsequent response. One of the major questions raised in this model is at what point we determine treatment failure or success. In this model we can mistakenly classify the animal as a treatment failure if we determine response too soon after instituting therapy.
However, the longer we wait the more we risk irreparable damage to the lungs causing the animal to become a respiratory chronic. In truth there is no way of knowing whether an animal is in fact a non-responder to treatment A or if the animal will respond over time. One solution is to institute a post-treatment moratorium which may be determined by the duration of plasma drug concentrations. We will discuss this approach later in this presentation.

Figure 4 depicts the likely scenario that would arise with the emergence of antimicrobial resistant pathogens. Eventually this may give rise to failures and relapses that could be associated with the emergence of resistance. This situation is also troublesome when the resistance is acquired in “unintended” targets particularly gastrointestinal pathogens. This situation may cause serious food safety concerns should food of animal origin be contaminated with faecal material containing resistant bacteria.

**Figure 4.**

There are several key questions that must be considered when we are considering the interaction between the antimicrobial and the target organism:

- How should we describe drug concentrations?
- How antimicrobials are best presented to the target pathogen?
- What is the target MIC for the pathogen?
- Then... can we put these together to predict when we should retreat a non-responding animal?

So, when we put this all together, what kind of predictions can we make about how long we can wait before we retreat an animal?
Figure 5 depicts the current suggested minimum and maximum times before moving to additional therapy in non-responding BRD cases. Suggested time periods are days (24 hour periods) after the only or last administration.

EVIDENCE-BASED EXAMPLES

Study 1: Tulathromycin Post-Treatment Interval

- Crossbred heifer feeder calves with a mean BW of 473 lbs (range 324 to 640 lbs) originating from MO, AR, KY, and TN.
- Entrance into the study required a combination of a clinical condition score of 1, 2, or 3 on a 0–4 scale combined with a rectal temperature ≥ 104.0°F.
- Label administration of tulathromycin (Draxxin®, Pfizer Animal Health).
- Cattle meeting entrance criteria were randomly assigned to a 7, 10, or 14 day post-treatment interval before they were eligible for further treatment.

Results: Treatment success (%) following a 7, 10 and 14 day post-treatment interval was 85.9, 85.3 and 88.8% respectively. This coincided with the period of detectable tulathromycin lung concentrations.
Study 2: Tilmicosin Post-treatment Interval
- Crossbred steer calves weighing from 402 to 706 lbs from CO, KS, OK and WY were enrolled in this study conducted in Wellington, CO.
- Animals with a clinical score of ≥ 2 on a scale of 1–5 combined with a rectal temperature of ≥ 104.0°F were admitted to the study.
- Treated with tilmicosin phosphate (Micotil®, Elanco Animal Health) according to label directions.
- Cattle were randomly assigned to treatment groups consisting of 3-, 5-, or 7-day post-treatment intervals.

Results: Treatment success (%) following a 3, 5 and 7 day post-treatment interval was 67.9, 73.0 and 86.9% respectively. This DID NOT coincide with the period of detectable tilmicosin serum and lung concentrations suggesting that drug concentration was not predictive of treatment success.

Study 3: Enrofloxacin Post-treatment Interval
- 12.5 mg/kg SC is back at a mean concentration of 0.06 µg/ml in the serum by 24 hours. Mean Cmax is 1.9 µg/ml.
- MIC90 of Mannheimia haemolytica reported as 0.06 µg/ml.
- Yet, enrofloxacin performed equally to a long-acting drug in a 7-day moratorium study.

Take Home Message
Plasma or tissue drug concentration is not always predictive of therapeutic success. Therefore ultra-long acting antimicrobials may not offer substantial benefits over drugs with shorter plasma T½. We do not know what the long term effect of these drugs will be on bacterial populations.

In bovine respiratory disease we are in effect treating 3 distinct populations of cattle:
- Cattle that will spontaneously respond to treatment.
- Cattle that will respond with the help of an antimicrobial.
- Cattle that aren’t going to respond no matter what therapy is used.

The key is determining which population you are examining in your practice.

Using Mixed Treatment Comparison Meta-Analysis to Compare Antibiotic Treatment for Bovine Respiratory Disease
- Most trials in the US for drug registration are comparison of non-active group versus active group.
- For Bovine Respiratory Disease non-active controls are non-ethical, non-viable, non-economical treatment choices for producers or vets.
- Producers and vets need to compare between current choices.
- 17 products registered for treatment of non-specific bovine respiratory disease in feedlot cattle in USA.
- Two new products (Gamithromycin and Tildipirosin) released this year.
- Is there a way we can compare these new drugs with existing drugs in the absence of direct comparison trials?
BRD Example

- North American based feedlot cattle entering at weight 400–700 lbs - no metaphylaxis (mass medication).
- The analysis used data from 93 trials from manuscripts and FDA reports, 194 arms of data.
- 12 active treatments.
- FDA summaries contained 5 three-arm trials; the remaining trials were two-arm trials.
- Sixty trials were active to non-active control comparisons.
- Thirty-three trials were active-to-active comparisons.
Drug ranking

Antimicrobial Therapy of Bovine Mastitis
Hans Coetzee, BVSc, Cert CHP, PhD, DACVCP
Associate Professor, Iowa State University, IA, USA

Bovine mastitis remains the most economically important infectious disease affecting dairy production worldwide. Antimicrobials are an essential component of mastitis therapy; but have you ever wondered how much difference these really make? The goal of this session is to help veterinarians better interpret antimicrobial susceptibility results as these pertain to mastitis pathogens. This information may help temper client expectations regarding the likelihood for treatment success.

When considering any infectious disease, an epidemiological approach would be to look at the relationship between the host, the pathogen and the environment (the epidemiological triad). Bovine mastitis is no different. One theme that will be repeated throughout this conference is that the solution to any production disease does not lie in a syringe. We must consider all other factors (host immune status, stage of production, management, causative agent) before we can offer our clients realistic expectations of the likelihood of treatment success.

Clinical pharmacologists may consider “the triad” a little differently. When examining antimicrobial therapy of any infectious disease, disease outcome could be determined by: 1) the disease process (location, pathogen and disease progression), 2) the host (husbandry, immunity) and 3) therapy (antimicrobials, anti-inflammatories and physiological state). A classic example of the clinical
pharmacologists’ triad in action would be therapy of subclinical mastitis caused by *Staphylococcus aureus*. In this case treatment success is complicated by: 1) the location of the organism in micro-abscesses and a disease progression that is frequently chronic, 2) a host immune response that is ineffective in clearing the infection and management practices that promote transmission and 3) therapy that doesn’t reach the site of infection in high enough concentrations to eliminate the infection. The situation is further confounded by the complex relationship between these factors resulting in a tangled web that can rarely be resolved by drug administration alone.

With this in mind let us consider the 5 major clinical presentations of mastitis in dairy cows and a treatment approach to each. 1) Toxic, or 2) gangrenous mastitis associated with *E. coli*, *Klebsiella* or *Staphylococcus aureus* infections are usually treated with a combination of fluids, antimicrobials, non-steroidal anti-inflammatory drugs (NSAIDS) and supportive care (stripping out, vitamin B) (F.A.N.S). In cases where irreparable damage to the udder has occurred these cows are usually culled. 3) Clinical mastitis is usually treated with intramammary antimicrobials and cows are milked last to prevent transmission to other cows or violative milk residues. 4) Subclinical, and 5) chronic mastitis cases are frequently treated with a combination of intramammary and systemic antimicrobials during lactation or the dry period. In these cases conventional therapy is frequently unsuccessful. As a last resort, producers may revert to permanently drying off the quarters by administering 120 ml chlorhexidine after two milkings 24 hours apart (Middleton, Fox. *National Mastitis Council Annual Meeting Proceedings*. 1999:231) prior to culling.

Once we have realistic expectations of the likelihood of therapeutic success following antimicrobial therapy of bovine mastitis, how do we decide which is the most appropriate antimicrobial treatment? One approach I like to use is the acronym S.P.A.C.E. This stands for:

- **Susceptibility**: Is the drug effective against the bug?
- **Pharmacokinetics/Dynamics**: Can the drug be maintained above the minimum inhibitory concentration (MIC) for long enough at the site of infection to be effective?
- **Adverse Reactions**: Is it safe to use this drug in this animal?
- **Compliance**: Can the owner comply with the prescribed regimen (drug dose, route duration, frequency, withdrawal period)?
- **Environment**: Where is the drug expected to work (aerobe/ anaerobe/ pus/ acid/ base)?

**Bacterial Culture and Antimicrobial Susceptibility Testing**

In the United States it has become popular for large dairy practices to perform their own antimicrobial culture and sensitivity tests. However in Northern Ireland it would most likely be more economical to submit samples to VSD Stormont. Regardless of who conducts the test, interpretation of culture results can still be a major challenge for practitioners. The following is one approach to interpreting bacterial culture results:

1. A pure culture of any mastitis pathogen should be considered highly significant. This includes cultures of *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus uberis*, *Streptococcus dysgalactiae*. 
2. Cultures of the following organisms should be considered contaminated at the time of collection and should be interpreted with caution. Mixed *E.coli* infections/*Bacillus* sp/*Proteus*/*S. faecalis*.

3. If the culture yields no growth (1/3 of cases) it does not mean that the animal does not have mastitis. No growth could be interpreted as one of the following scenarios:
   a. The cow is an intermittent excretor of bacteria. This occurs frequently with *Staphylococcus aureus*.
   b. The cow was treated with an antimicrobial prior to sample collection.
   c. The milk sample was not handled correctly.
   d. The cow is infected with an unusual organism that either does not grow or grows very slowly in conventional culture systems. Some examples include *Mycoplasma* spp. and *Prototheca* spp.

**MINIMUM INHIBITORY CONCENTRATION (MIC) AND BREAKPOINTS**

In addition to bacterial identification, culture results will frequently report the results of antimicrobial sensitivity testing in the form of the minimum inhibitory concentration (MIC). The MIC is the antimicrobial concentration required to inhibit bacterial growth in-vitro (hopefully under standardized conditions) for a standardized time period.

Traditionally the MIC has been determined by plating a standardized amount of bacterial inoculum on a Kirby-Bauer plate and measuring the zones of inhibition around antimicrobial impregnated discs. Although it is tempting to base decision on which drug to use based on the largest zone of inhibition, this approach is incorrect. Firstly, antimicrobials do not diffuse at the same rate through agar therefore a significant “grey area” exists at the edge of the zone of inhibition. The zone of inhibition may therefore be a function of drug diffusion rate rather than an accurate representation of likely clinical efficacy. Furthermore, the difference between a bacteria being designated as susceptible or intermediately susceptible, or intermediately susceptible and resistant may only be 1 mm. This is a fairly imprecise measure given that many zones of inhibition are surrounded by a “feather” edge. Kirby-Bauer results should therefore be interpreted with caution.

A more precise measure of susceptibility is serial dilution susceptibility testing. In this test a fixed amount of bacteria is inoculated into broth containing doubling dilutions of antimicrobials typically 0.25, 0.5, 1, 2, 4, 8 and 16 $\mu$g/mL. The MIC is designated as the lowest concentration where no visible growth of bacteria is detected in the broth media after a designated period of time. The results of broth dilution testing are correlated back to the Kirby-Bauer disc diffusion test using a statistical process called error rate bounding.

MIC determination has been extended in recent years by the United States Clinical and Laboratory Standards Institute (CLSI) to include the concept of a breakpoint. A breakpoint expands upon the MIC concentration to predict clinical outcome for a specific pathogen, associated with a specific disease, in a specific species, given a specific regimen.

A **breakpoint** is therefore a specific MIC of a drug selected to predict clinical outcome for a:

1. A specific pathogen
2. Associated with a specific disease
3. In a specific species
4. Given a specific regimen (dose, route, duration, frequency)

   Similar to the MIC, a **breakpoint** is selected to designate a susceptible (S), intermediate susceptibility (I), and resistant (R) classification however some drug/pathogen combinations only have a susceptible and resistant breakpoint.

**The breakpoint uses the laboratory MIC to predict CLINICAL efficacy in the animal.**

**INTRAMAMMARY ANTIMICROBIALS WITH VALIDATED VETERINARY BREAKPOINTS FOR MASTITIS**

**Lactating Cows**
- Pirlimycin (Pirsue, Pfizer Animal Health)
  - *Staphylococcus* species
  - *Streptococcus* species
- Novobiocin and penicillin
- Ceftiofur Intramammary

**Dry Cows**
- Novobiocin and penicillin
  - *Staph aureus*
  - *Strep agalactiae*
  - *Strep dysgalactiae*
  - *Strep uberis*
  - “Other”

**Take Home Message**
Making treatment decisions based on MIC’s of drugs with validated veterinary breakpoints for mastitis should increase the likelihood of a favourable therapeutic outcome provided you use the approved dose, route, duration and frequency of administration.

**UNFORTUNATELY MASTITIS THERAPY IS NEVER THIS SIMPLE!**
Hoe and Ruegg (*JAVMA*. 2005;227(9):1461–1468) found no association between clinical outcome and antimicrobial susceptibility results in a study with cows having a mild to moderate mastitis. These were treated with Pirlimycin SID for 2 days. Duration of therapy and days to clinical cure were no different regardless of whether susceptibility results were S or R. Bacteriological cure rate was no different for S and R bacteria.

   Based on these findings and other reports questioning the predictive value of susceptibility testing, the following guidelines have been developed for how to interpret what an “S” means clinically for a mastitis pathogen.

**ONLY if a drug has a CLSI approved breakpoint and...**
1. The susceptibility result is “S”,
2. The cow is in her 1st or 2nd lactation, and
3. Only one quarter is affected, then...
   - *Staphylococcus aureus*: 50–60% cure rate, otherwise cull or dry cow therapy
   - Coagulase negative *Staphs*: 60–80% cure rate
   - *Strep agalactiae*: 90–100% cure rate
   - Environmental *Streps*: 60–65% cure rate, there is true resistance in this group
   - *E. coli*: 80%, more serious in younger cows

In addition to knowing the susceptibility of an organism to a given range of antimicrobials, bacterial culture also allows you to narrow down which antimicrobials are likely to be effective against a particular pathogen. It’s important to recognize that beta-lactam antimicrobials (penicillins) are not very effective against gram-negative infections. Pirlimycin and erythromycin also have no gram-negative activity. This should be considered when selecting drugs to treat these infections.

**How Much Difference Does An Intramammary Antimicrobial Make?**
A study involving 352 cows conducted at 13 trial sites submitted to the US Food and Drug Administration was conducted to determine the efficacy of ceftiofur intramammary infusion against field cases of clinical mastitis. Primary inclusion criteria were the presence of visually abnormal milk (clots/ flakes/ watery secretions). Cows were treated with ceftiofur IMM solution containing either 0 mg; 62.5 mg or 125 mg of ceftiofur.

<table>
<thead>
<tr>
<th>Type of cure</th>
<th>Treatment</th>
<th>Cure rate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>0 mg</td>
<td>64/117 = 54.7%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>62.5 mg</td>
<td>75/108 = 69.4%</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>125 mg</td>
<td>88/112 = 78.6%</td>
<td>0.002</td>
</tr>
<tr>
<td>Bacterial</td>
<td>0 mg</td>
<td>19/46 = 41.3%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>62.5 mg</td>
<td>21/46 = 45.6%</td>
<td>0.356</td>
</tr>
<tr>
<td></td>
<td>125 mg</td>
<td>38/54 = 70.4%</td>
<td>0.006</td>
</tr>
<tr>
<td>Protocol</td>
<td>0 mg</td>
<td>11/46 = 23.9%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>62.5 mg</td>
<td>19/46 = 41.3%</td>
<td>0.068</td>
</tr>
<tr>
<td></td>
<td>125 mg</td>
<td>34/54 = 63.0%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Source: FOI, Available at www.fda.gov/cvm/FOI/141-238020905.pdf

Cows not receiving any active ingredient had a 54.7% clinical cure rate and a 41.3% bacterial cure rate. These data suggest that while intramammary antimicrobials hasten recovery in cases of clinical mastitis, over 50% of cows will show clinical recovery without treatment.

**What About Systemic Treatment with Ceftiofur for Staphylococcus aureus Infections?**
Systemic ceftiofur is frequently considered ineffective against intramammary infection because it is thought that distribution into milk is poor. This is evidenced by a zero milk withdrawal period. However, *Staphylococcus aureus* infections are not in the milk but rather are located in the udder parenchyma.
This does not mean that ceftiofur should be considered as a possible therapeutic option for use in combination with intramammary cephalosporin administration.

Ceftiofur is very rapidly metabolized in the liver to an active metabolite desfuroylceftiofur (DFC). In fact, none of the parent ceftiofur can be detected in the plasma 1 hour after intramuscular administration. The MIC90 of ceftiofur against staphylococcal infections is 1.0 μg/mL. However the MIC90 of DFC against staphylococcal infections is 8 μg/mL. Therefore, a much higher concentration of the active metabolite is required to be effective against Staphylococcus aureus than the parent compound (Salmon SA, Watts JL, Yancey RL Jr. In vitro activity of ceftiofur and its primary metabolite, desfuroylceftiofur, against organisms of veterinary importance. J Vet Diag Invest. 1996;8:332–336). This concentration is not readily achieved in biological matrices. Therefore ceftiofur would not be a good choice against Staphylococcus aureus infections.

What About Other Systemic Drugs Treatments?
Nickerson et al (J Dairy Sci. 1999;82(4):696–703) conducted a study to evaluate the efficacy of tilmicosin injection administered at dry-off against Staphylococcus aureus at 28 days postcalving. 44 cows with at least one naturally or experimentally infected quarter were assigned to one of three treatment groups. Group 1 received an intramammary infusion of cepahapirin at 10 ml/quarter; Group 2 received 1,500 mg tilmicosin infused into the quarter and Group 3 received a single subcutaneous injection of tilmicosin at 5 mg/kg at drying off and 4 days later. Results demonstrated the following percentage cures for IMI caused by Staph aureus at 28 d postcalving based on individual mammary quarters: cepahapirin benzathine, 78.1%; tilmicosin infused, 74.2%; and tilmicosin injected, 9.1%.

During the first 4 wk after drying off, the mean concentration of tilmicosin in mammary secretions from cows infused with the antibiotic remained approximately 10-fold higher than that in secretions from cows injected with the antibiotic (3.43 vs. 0.32 ppm), and, by the time of calving, concentrations for cows treated with both methods were below the dilution limit of the assay (< 0.1 ppm). Results demonstrated that intramammary infusion of tilmicosin was equally as effective as cepahapirin benzathine in curing IMI caused by Staph aureus at drying off; however, the subcutaneous injection of tilmicosin at the dose used was not effective as a dry cow therapeutic against Staph aureus.

What’s New in the World of Streptococcus uberis Therapy?
Hillerton and Kliem (2002) examined treatment of Streptococcus uberis clinical mastitis to minimize the use of antibiotics (Journal of Dairy Science. 2002;85(4):1009–1014). Antibiotic regimens (intramammary antibiotic, penicillin-based parenteral treatment) and intramuscular oxytocin were tested for effectiveness against experimental infection by Streptococcus uberis with the following results from 54 animals: 1) no treatment led to deterioration of infected quarters, requiring intervention within 48 h for cow health; 2) aggressive intramammary antibiotic at every milking achieved 70% clinical cure in 3 d and 100% cure within 6 d; overall bacteriological cure was 80%; 3) parenteral treatment alone used about 14 times as much antibiotic with 18% clinical cure in 3 d and 91% within 6 d; overall bacteriological cure was 80%; 4) combination of aggressive intramammary and parenteral treatments achieved 61% clinical cure in 3 d and 100% within 6 d; overall bacteriological cure was 72%; 5) intramammary antibiotic at labeled rates (1x for 3 d) achieved 27% clinical cure in 3 d but 91% within 6 d of treatment; overall
bacteriological cure was 64%; 6) use of oxytocin alone for 3 d failed to achieve clinical improvement with an increase in the severity of mastitis; g) combining oxytocin with labeled use of intramammary antibiotic (1x for 3 d) was unsuccessful: 0% clinical cures in 3 d, 10% in 6 d; significantly poorer than intramammary antibiotic alone. Extended treatment periods with parenteral or intramammary antibiotics resulted in positive inhibitory tests for milk from individual quarters up to 8 d after treatment. Aggressive intramammary antibiotic was the most effective treatment for fastest cure clinically and bacteriologically using least antibiotic.

Table 1. The clinical cure achieved for each of seven treatments of *Streptococcus uberis* mastitis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. quarters</th>
<th>3 days (%)</th>
<th>6 days (%)</th>
<th>Total (%)</th>
<th>None (%)</th>
<th>% cured in total</th>
<th>Mean no. treatments</th>
<th>Mean time (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment (NT)</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>7.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Intramammary (A)</td>
<td>10</td>
<td>7 (70b)</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Parenteral (P)</td>
<td>11</td>
<td>2 (18a)</td>
<td>8</td>
<td>91</td>
<td>0</td>
<td>91</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Combined (A + P)</td>
<td>18</td>
<td>11 (61b)</td>
<td>7</td>
<td>150</td>
<td>0</td>
<td>6.8 (syringes)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Intramammary (L)</td>
<td>11</td>
<td>3 (27a)</td>
<td>7</td>
<td>91</td>
<td>0</td>
<td>100</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Oxytocin (O)</td>
<td>10</td>
<td>0 (0a)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Combined (O + L)</td>
<td>10</td>
<td>0 (0a)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Where Parenteral and Oxytocin were treatments every 24 h and Aggressive and Oxytocin were treatments every milking. The first four treatments were examined in phases 1 and 2 of the experiment and the last three treatments were examined in phase 3 of the experiment.

2 Statistically significant differences (P < 0.001) on the amount of clinical cure within each column and only within each section, i.e., phase of the experiment, of the table are shown by use of different superscripts (a vs. b and e vs. f). No comparisons across columns have been made.

Table 2. The amount of bacteriological cure (for those quarters cured clinically) achieved for each of seven treatments of *Streptococcus uberis* mastitis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No quarters clinically cured</th>
<th>3 d (%)</th>
<th>6 d (%)</th>
<th>Total (%)</th>
<th>No cure (%)</th>
<th>% Cured of all quarters infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment (NT)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Intramammary (A)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Parenteral (P)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Combined (A + P)</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Intramammary (L)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Oxytocin (O)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Combined (O + L)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

1 Where Parenteral and Parenteral were treatments every 24 h and Aggressive and Oxytocin were treatments every milking. The first four treatments were examined in phases 1 and 2 of the experiment and the last three treatments were examined in phase 3 of the experiment.

2 Statistically significant differences (P < 0.005) on the amount of bacteriological cure within each column and only within each section, i.e., phase of the experiment, of the table are shown by use of different superscripts (a vs. b and e vs. f). No comparisons across columns have been made.

**DO WE NEED TO COVER GRAM-NEGATIVE BACTERIA DURING THE DRY PERIOD?**

Bradley & Green (*JDS*. 2001;83:1957–1965) reported that 52% of clinical coliform mastitis in the 1st 100 days of lactation is acquired in the dry period. In a subsequent report, 41% of all cases of *E. coli* mastitis were found to occur in less than 3% of the population (Bradley, Green *J Clin Micro*. 2001;39(5):1845–1849). 24% of clinical *E. coli* mastitis cases were recurrent cases in the same quarter. 86% recurrent *E.
coli mastitis involved the same genotype. Therefore it is reasonable to conclude that *E. coli* can persist in the mammary environment. Thus using an antimicrobial with adequate gram-negative spectrum during the dry period appears to be rational.
Ancillary Therapy of Pneumonia and Endotoxic Mastitis
Hans Coetzee¹, BVSc, Cert CHP, PhD, DACVCP; Mike Apley, DVM, PhD, DACVCP
¹Associate Professor, Iowa State University, IA, USA

Is there something we can add to make the antimicrobials work better? The veterinary tendency towards polypharmacy is supremely illustrated in the therapy of bovine respiratory disease (BRD) and toxic mastitis in dairy cattle. This session focuses on adding an anti-inflammatory (a steroids or non-steroidal anti-inflammatory drug (NSAID) to treatment regimens in an effort to improve treatment response. The goal is to establish if we have any evidence aside from “they look better faster” to suggest that ancillary therapy represents a quantifiable economic benefit to our producers.

We will start with a brief overview of how anti-inflammatory drugs work:

We will now look at the different classes of anti-inflammatory drugs available for use in food animals.
GLUCOCORTICOSTEROIDS

Overview
Glucocorticoids inhibit the production of inflammatory molecules such as cytokines and adhesion molecules. These enable inflammatory cells to leave the blood stream and enter the site of inflammation. Glucocorticoids also maintain membrane integrity and exert a host of effects of protein, lipid and carbohydrate metabolism.

Dexamethasone is the most widely used glucocorticosteroid in production animal medicine. Glucocorticosteroids prevent arachidonic acid release by stabilizing cell membranes and inducing lipocortin production. Lipocortin prevents phospholipase A2 from encountering cell membrane associated arachidonic acid. This reduces the availability of precursors for prostaglandin production. Glucocorticoids need to be administered early in the course of disease for maximum efficacy. Arachidonic acid release occurs early in the cascade of events following a traumatic incident or endotoxin exposure. Once arachidonic acid is released, lipooxygenase and cyclooxygenase have the substrate required to form inflammatory intermediates.

Glucocorticoid drugs are also known to inhibit the production of cyclooxygenase 2 (COX-2) which produces inflammatory prostaglandin from arachidonic acid. Steroids have not been observed to inhibit COX-1, a constitutive enzyme which is responsible for producing “housekeeping” prostaglandins in the kidney and gastric mucosa.

GLUCOCORTICOSTEROIDS AND EBM
1. Bovine Respiratory Disease
Twenty-five years after publication of the study described here, it is still the only clinical trial addressing the use of steroids for ancillary therapy of BRD as you would encounter it clinically in the United States.1 One of two treatments was administered to animals identified as displaying clinical signs of BRD. Common drugs for the two treatment groups included IV oxytetracycline (5 mg/lb) and IM pyrelamine (250 mg total dose) on a daily basis for 3 days. Treatment group 1 also received 20 mg dexamethasone every day while treatment group 2 received a 10 ml placebo injection. The same treatments for each group were continued through day 9, as needed, for non-responders. Response was significantly different at P ≤ 0.05 and relapse rate was significantly different at P ≤ 0.01.

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>Treatment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number treated</td>
<td>1113</td>
</tr>
<tr>
<td>Number responding</td>
<td>913 (82%)</td>
</tr>
<tr>
<td>Death loss</td>
<td>77 (6.9%)</td>
</tr>
<tr>
<td>Relapses</td>
<td>265 (23.8%)</td>
</tr>
</tbody>
</table>

These findings aren’t that surprising since dexamethasone, at 0.4 mg/kg daily (0.9 ml/100 lbs of a 2 mg/ml solution) for 3 days, is used as a research model to suppress neutrophil function in cattle.2 This model was utilized in small Holstein calves in conjunction with induced Haemophilus somnus pneumonia to demonstrate that this dexamethasone regimen increased lung lesions.3 An IBR latency model in
rabbits demonstrated that a single high-dose injection of dexamethasone (2.8 mg/kg) could bring about reactivation of latent BHV-1.4

Other studies have failed to show significant differences in treatment response using prednisone acetate, methyl prednisolone, or methyl-prednisolone-succinate in natural and induced respiratory disease.5,6

Conclusions
Lack of supporting data hasn’t appeared to impede the anecdotal use of steroids in the therapy of BRD. We have been shocked at the use of steroids in compounded preparations for multiple days for therapy of BRD, especially in small calves. This use is absolutely inappropriate. What about a one-time use at the beginning of therapy at a reasonable dose (1 ml/100 lbs of a 2 mg/ml dexamethasone solution)? Without knowing the exact dose for reactiving latent IBR in cattle, it could be a possibility.

Outside of anecdotal observations that the cattle “look better faster”, there are no data to support an improvement in clinical response in light of potential adverse effects.

2. Mastitis

Study 1: 30 mg Dexamethasone IM to cows immediately following induction of E. coli into the mammary gland.12

Results: Reduced mammary gland swelling. Maintained rumen motility. Higher rectal temperatures when compared with untreated controls. Higher milk production when compared with untreated controls (reduced losses).

Study 2: 0.44 mg/kg (220 mg/500 kg cow) 2 hours following introduction of purified endotoxin into mammary gland. Mammary gland swelling was evident at treatment but no other systemic signs were evident.13

Results: Higher dose also relieved swelling of mammary gland. Lower rectal temperatures when compared with controls. Lower milk production (increased losses).

Study 3: 20 mg isoflupredone acetate IV administered after the development of clinical signs of mastitis induced by intramammary infusion of endotoxin.

Results: No measurable differences in heart rate, rectal temperature, rumen motility or mammary gland surface area in 14 hours following endotoxin infusion. No difference in milk production between treated and untreated cows.

Conclusion
Cattle are sensitive to glucocorticoid-induced immune suppression. Both exogenously administered glucocorticoids and endogenous cortisol exhibit these effects. This assertion is supported by the observation that coliform intramammary infections are more severe in recently calved cows. It is however unlikely that one-time administration of a glucocorticoid will adversely affect cows with endotoxin induced severe clinical mastitis.

It is important to recognize that most cows with endotoxic mastitis usually have achieved peak bacterial numbers by the time the disease manifests itself clinically. Neutrophil migration into the
mammary gland may therefore have peaked by the time these drugs are administered. Accordingly, the impact of steroid administration on immune function may be less deleterious if the drugs are administered once clinical signs are observed.

Many of the potential benefits of steroid administration such as sustained rumen motility and increased milk production were observed in artificial infection models. In these studies glucocorticoids were administered at the time of infection or immediately following infection. In the clinical setting ancillary therapy is only likely to be instituted once clinical signs have appeared. Unfortunately there are very few studies that have evaluated glucocorticoids under typical field conditions.

In the absence of clear contraindications and in light of the potential beneficial effects of glucocorticoid therapy in the treatment of endotoxic mastitis, the one-time use of these drugs as part of a treatment regimen may be a rational consideration. Both dexamethasone and isoflupredone acetate are labeled for use in dairy cattle without milk discard. These compounds are also relatively inexpensive. It the absence of clear experimental data to support this application in a clinical setting, it would be reasonable to administer this treatment to severe cases as a single injection early in the course of the disease.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Overview
The primary mode of action of NSAIDs currently used in food animals is to inhibit the synthesis of prostaglandins (PG) and thromboxanes through the inhibition of cyclo-oxygenase (COX). Cyclo-oxygenase is composed of 2 isoforms, COX-1 and COX-2. COX-1 is the “housekeeping” isoform that mediates the formation of constitutive prostaglandins. PG’s generated by COX-1 are constantly present, providing homeostasis. These include protection of the GIT mucosa, hemostasis and protection of the kidney against hypotension. COX-2 is the highly “inducible” isoform that is dramatically up regulated in the presence of inflammation.

All NSAIDs that are commonly used in production animals inhibit both COX isoforms and consequently the formation of PG E2 in the brain, which effectively reduces fever. Aspirin and Flunixin meglumine are the only NSAIDs labeled for use in cattle in the United States. Other compounds that are approved in Europe and which may become available for use in food animals over the next 5 to 10 years include carprofen, meloxicam, ketoprofen and tolifenamic acid.

NSAIDs AND EBM

Flunixin Meglumine

1. Bovine Respiratory Disease
The NSAID currently labeled specifically for BRD in the United States in Flunixin meglumine (Banamine® Injectable Solution, Schering-Plough Animal Health). The label includes indications for the control of pyrexia associated with bovine respiratory disease and endotoxemia. The inflammation indication on the label is for the control of inflammation in endotoxemia. Flunixin meglumine is considered an effective analgesic, antiinflammatory, and antipyretic. The mechanism of action is cyclooxygenase inhibition.
The outlines below summarize published studies and the Freedom of Information (FOI) summaries of flunixin meglumine effects on respiratory disease outcome.

**Study 1: 12 week old dairy calves, induced *Pasteurella haemolytica* pneumonia.**
Four treatment groups: No treatment, oxytetracycline (10 mg/kg IM SID for 3 days), flunixin meglumine (2.2 mg/kg IV SID for 3 days), and both oxytetracycline and flunixin meglumine.

Results:
- **OTC alone** reduced the number of calves with fevers and tachypnea and reduced the extent and severity of fibrinous pneumonia as compared to the controls (no mortality).
- **Flunixin alone** had no antipyretic effect and no reduction in severity of *Pasteurella* pneumonia compared to the control calves although fewer calves were noted with tachypnea. (1 dead out of 8).
- **OTC and flunixin combined** had no evident macroscopic consolidation in the lungs, rectal temperature dropped more quickly than in any of the other three groups (no mortality).

**Study 2: 12-week-old calves, PI3 virus administered into the upper airways.**
Two treatment groups: Flunixin meglumine (2.2 mg/kg IV SID for 3 days) and controls.

Results: Flunixin reduced the number of calves with fever (> 39.7°C), and the number of calves with tachypnea as compared to untreated controls. There was a marked decrease in pulmonary consolidation in the treated group.

**Study 3: Calves receiving 3 methylindole (3MI) intratracheally.**
Two treatment groups: Flunixin meglumine (2.2 mg/kg) on the mornings of days 1, 2, and 3 when they started displaying respiratory rates twice that of baseline, and negative controls.

Results: Respiratory rates of the treated calves did not significantly differ from that of environmental controls which did not receive the 3MI, while the untreated calves which received 3MI had significantly elevated respiratory rates. Flunixin calves had much less pronounced alveolar epithelial hyperplasia as compared to controls.

**Study 4: Housed beef calves, undifferentiated respiratory disease (a rectal temperature > 39.5°C, respiratory rate > 30/minute, and an increased respiratory effort).** Further treatment based on a rectal temperature of 39.5°C on day 4.
Two treatment groups: Tilmicosin phosphate (10 mg/kg SC, once) vs. therapy with tilmicosin phosphate (10 mg/kg SC, once) combined with flunixin meglumine (2.2 mg/kg IV, once).

Results: 17/51 tilmicosin calves (27.9%) required further therapy while 9/58 tilmicosin/flunixin calves (15.5%) were treated again. This difference was not significant. No mortalities occurred.

**Study 5: Freedom of Information Summary study. 363 calves (heifers, steers, and bulls) 6–12 months old (mean weight 420 lbs.) at 3 locations. Naturally occurring respiratory disease.**
Two treatment groups: OTC injectable solution administered for 3 consecutive days at 10 mg/kg (4.5 mg/lb.) IM, as compared to OTC injectable solution (as above) plus flunixin meglumine at 2.2 mg/kg SID for 1–3 days (administered again on days 2 and 3 if temp. not below 104.0°F).
Duration of study: 10 days, treatment failure was defined as developing severe recurrent respiratory disease (score of 3 or more on scale of 0 = normal, 1 = slightly ill, 2 = moderately ill, 3 = very ill, and 4 = moribund) from the end of the 3 days of treatment to the end of the study.

Results:

- Mortality: 15/182 dead in OTC alone, 8/181 died in OTC/flunixin group. One site had 1 mortality in the OTC group, one site had one dead in the OTC/flunixin group, and one site had a concurrent BVD outbreak with 14 dead in the OTC group and 7 dead in the OTC/flunixin group. Not statistically significant.
- Character of respiration: No significant difference at pretreatment (day 0) and on day 1. OTC/f group was better on days 2 and 4. On day 9, 99/144 (69%) of the OTC/f calves had normal respiration compared to 70/139 (50%) in the OTC group.
- Illness index scores: More OTC/f animals scored normal on days 1–9. Statistically significant?
- Rectal temperature: Statistically significant difference in temperature decrease on day 1, with OTC/f group having a greater decrease. No significant differences on other study days.
- Depression: Fewer depressed animals in OTC/f group.
- Treatment success/failure: 47/179 (26%) failures in OTC group, 40/181 (22%) in OTC/f group. Not statistically significant.
- Lung pathology: Little or no difference in lung pathology between groups.
- Weight gain and daily feed intake: OTC group numerically superior to OTC/f group (16.5 lbs. vs. 10.6 lbs. respectively) but this was not significantly significant.

Study 6: Freedom of Information Summary #2. 81 male Holstein calves (304 months, mean 82.3 kg) with naturally occurring BRD (acute clinical signs of pneumonia with elevated rectal temp $\geq$ 104.0°F and respiratory rate $\geq$ 40/minute).

Two treatments: OTC injectable solution administered for 3 consecutive days at 10 mg/kg (4.5 mg/lb.) IM, as compared to OTC injectable solution (as above) plus flunixin meglumine at 2.2 mg/kg SID for 1–3 days (administered again on days 2 and 3 if temp. not below 104.0°F).

Results:

- Number of flunixin treatments: 58.1% of OTC/f calves required one flunixin meglumine injection, 34.9% required a second, 7% required a third.
- Mortality: No deaths during the study.
- Character of respiration: For days 2–7, more animals in OTC/f group had normal respiration than did the OTC group. Statistically significant?
- Illness index scores: More normal animals in OTC/f group on days 2 and 3. Statistically significant.
- Rectal temperature: Statistically significant advantage to OTC/f group on days 1, 2, and 3.
- Depression: Improved demeanor in OTC/f group on days 2–7. Statistically significant?
- Treatment success/failure: 40% treatment failures in OTC/f group, 47% treatment failures in OTC group. 44% of the OTC treatment group occurred on day 3, while 24% of the OTC/f treatment failures occurred on day 3.
- Weight gain: 4.6 kg for OTC/f, 4.0 KG for OTC. Not statistically significant.
What about other NSAIDs for ancillary therapy of BRD? If there is published evidence that phenylbutazone or aspirin change therapeutic outcome in BRD therapy we have not been able to find it. The pharmacokinetics, published anti-inflammatory effects in cattle, and dosing strategies of these compounds in cattle have been previously summarized. \textsuperscript{11} Practitioners should be aware that the residue potential of phenylbutazone in cattle is coming under increased scrutiny.

2. Mastitis
Recently the NSAID Flunixin meglumine (Banamine® Injectable Solution, Schering-Plough Animal Health) was labeled specifically for endotoxic mastitis in the United States. The label includes indications for the control of pyrexia associated with acute bovine mastitis. The inflammation indication on the label is for the control of inflammation in endotoxemia. There is a 36 hour milk withhold period after the last treatment.

The outlines below summarize the Freedom of Information (FOI) summaries and published studies of flunixin meglumine effects on acute mastitis outcome.

\textbf{Study 1: FOI Summary: Multi-site field trial in dairy cows with acute bovine mastitis.}
Design: 117 adult lactating dairy cows, mainly Holsteins divided into 2 treatment groups. 58 cows received flunixin at 2.2 mg/kg and 59 cows received saline IV.

Inclusion criteria: \( \geq 104 \) degrees F and showing at least 2 clinical signs of udder inflammation, swelling, pain or firmness. Test duration: 4 hours. Primary variables: Treatment success if body temperature decreased by \( \geq 2^\circ F \) or a decrease to normal (101.5\(^{\circ} F \) \textbf{4 hours after administration}). Udder inflammation was assessed on a 4 tier scale (normal, mild, moderate, severe).

Results: Only 40 cows in the analysis. Statistically significant \((p < 0.0001)\) reduction in pyrexia at 4 hours after administration (No assessment of fever at any other time points). No statistically significant difference in success rates for inflammation \((p = 0.0632)\). The only conclusion we can draw from this study is that Banamine reduces fever 4 hours after administration. We can draw no inferences from this in terms of reduced production losses or increased survival.

Objective: To determine the effects of 2 anti-inflammatory drugs in lactating Holstein cows with endotoxin-induced mastitis.

Animals: 30 multiparous Holstein cows that had been lactating for 30 to 60 days.

Procedure: Bacterial culture of milk samples and physical examinations established that study cows were in good health and free of mastitis. Mastitis was induced in 1 front mammary gland by intramammary administration of purified bacterial endotoxin. Cows were allocated into 1 of 3 treatment groups: untreated endotoxic mastitis (\( n = 9 \)), endotoxic mastitis plus flunixin meglumine (9), and endotoxic mastitis plus isoflupredone acetate (10). Heart rate, rectal temperature, mammary surface area, and rumen motility were recorded hourly for 14 hours following endotoxin administration. Flunixin meglumine or isoflupredone acetate was administered after mammary swelling and rectal temperature > or \( \geq 40 \) degrees C had developed. Milk production was evaluated from 5 days before to 10 days after induction of mastitis.
Results: Neither drug ameliorated loss of milk production or swelling of the affected mammary gland. Both drugs reduced mean heart rate during the 14 hours following endotoxin administration, compared with untreated control cows. Cows treated with flunixin meglumine had increased rumen motility and decreased rectal temperature during the same period, compared with all other cows.

Conclusions: Neither drug enhanced recovery of milk production following endotoxin-induced mastitis. Flunixin meglumine decreased rectal temperature, whereas isoflupredone did not; however, it has not been established that reduction of fever is beneficial to cows with naturally occurring mastitis.


During a three-year study, 54 cows with toxic mastitis were allocated randomly to one of three treatment groups (A, B and C). Each cow was re-examined within 24 hours of the initial examination, and, during this time, group A received fluid therapy (45 liters of intravenous isotonic electrolyte solution) and flunixin meglumine (2000 mg), group B received fluid therapy only, and group C received flunixin meglumine only. In addition all the cases were treated with parenteral and intramammary tetracyclines, oxytocin and calcium borogluconate. There was no significant difference in the rate of survival between the treatment groups and 29 of the cows (53.7 per cent, 95 per cent confidence interval of 39 to 67 per cent) survived.

**What About Other NSAIDs For Ancillary Therapy of Acute Mastitis?**

Aspirin, flunixin meglumine, phenylbutazone, carprofen, ibuprofen and ketoprofen have been studied as treatments of experimental coliform mastitis or endotoxin-induced mastitis.

Orally administered aspirin should be used with caution as a treatment of acute mastitis because many of these cases develop severe rumen atony. When used, FARAD recommends a milk and slaughter withdrawal interval of 24 hours to reduce the risk of Reye’s syndrome in children. Phenylbutazone has also been studied and widely used as treatment of acute mastitis; however the FDA-CVM has strongly discouraged its use in food animals. The tolerance level for phenulbutazone is zero and detection of any concentrations is an illegal residue.

Carprofen is a propionic acid derivative that demonstrates weak COX binding. This compound demonstrates age dependent pharmacokinetics with significantly longer elimination times is younger cattle. In Europe, the manufacturer claims that a single injection provides relief for up to 3 days in calves less than 12 months of age. A clinical trial was undertaken to investigate the efficacy of a single dose of carprofen (CPF) in the treatment of bovine respiratory disease in cattle. Tilmicosin was used as a basal treatment in all animals. Six hours after dosing, body temperature and respiratory rates in animals treated with CPF-tilmicosin had decreased and were significantly lower than in the animals treated with tilmicosin alone (P < 0.05). Over the period of clinical observation, CPF-tilmicosin treatment produced a clinical resolution of the pneumonia similar to treatment with tilmicosin alone. Meloxicam is a member of the oxicam class of NSAID’s. The elimination half time is 24 to 26 hours which has resulted in a “long-acting” label claim in the European Union. A recent report evaluating Meloxicam has provided, to our knowledge, the first evidence of a demonstrated economic benefit to using a NSAID in the treatment respiratory disease in feedlot cattle. Animals with clinical symptoms of BRD received 20 mg/kg oxytetracycline with either 0.5 mg/kg meloxicam or 0.9% isotonic saline. To
assess performance animals were weighed at 0, 7, 35, 70 and 105 days and finally before slaughter. Approximately 200 cattle with a mean body weight of 232 kg were evaluated. Mean body weight was significantly higher for the meloxicam treated cattle from Day 70 (p < 0.05) until slaughter (p < 0.01). The mean average daily gain until slaughter was significantly higher with 1.23 kg in the treated group compared with 1.12 kg in the control group (p < 0.01). The mean carcass weight of the meloxicam treated group was significantly greater than the control group (P < 0.05; 282.1 kg vs 269.8 kg). It was concluded that a single injection of meloxicam as adjunct therapy in BRD in feedlot cattle resulted in a substantial pharmaco-economic benefit.\textsuperscript{18}

The propionic acid NSAIDs (carprofen and ketoprofen) have good potential as treatments for severe gram-negative mastitis. The efficacy of ketoprofen in the treatment of acute clinical mastitis was evaluated in a clinical trial comprising a non-blind controlled study and a blind, placebo-controlled study. All the cows were treated with 20 g sulphadiazine and 4 g trimethoprim intramuscularly upon diagnosis, and half the dosage was given once daily thereafter. In addition, the ketoprofen treatment groups received 2 g ketoprofen intramuscularly once daily for the duration of the antimicrobial therapy.

Recovery rates for the non-blind contemporary controls and the blind placebo-controls were 83.7 per cent and 70.7 per cent, respectively. In the non-blind controlled ketoprofen and the placebo-controlled ketoprofen treatment groups, recovery rates were 94.7 per cent and 92.3 per cent, respectively. It was concluded that ketoprofen significantly improved recovery in clinical mastitis in dairy cows.\textsuperscript{15}

The pharmacodynamics of carprofen and its pharmacokinetics in plasma and milk of healthy cows and cows with endotoxin-induced mastitis were studied after a single intravenous dose of 0.7 mg/kg body weight. Carprofen was administered to five clinically healthy cows and to the same cows 3 weeks later, 2 h after intramammary infusion of endotoxin. Compared with the untreated mastitic controls, carprofen treatment significantly reduced heart rate (P < 0.01), rectal temperature (P < 0.001), quarter swelling (P < 0.01).\textsuperscript{16}

**References**


Treatment and Prevention of Calf Scours
Hans Coetzee, BVSc, Cert CHP, PhD, DACVCP
Associate Professor, Iowa State University, IA, USA

If your client was experiencing an outbreak of calf scours and had $500 to spend on treatment and prevention how would you advise him to spend his money? While antibiotic and vaccine sales are good for business, will these have the biggest impact on preventing the problem in the future? In this session we will critically evaluate the case for using antibiotics to treat calf diarrhoea and will introduce a few “novel” concepts on prevention including the “Sandhills Calving System”.

This session will be divided into 5 sections:
1. What is diarrhea?
2. Classification of fluid loss
3. Causative organisms
4. Consequences of fluid loss
5. Treatment and prevention

I. WHAT IS DIARRHOEA?
In its simplest form, neonatal calf diarrhoea or “calf scours” can be defined as a failure of net intestinal uptake of water and sodium such that the colon is overwhelmed. Essentially the gastrointestinal system is characterized by a “flux” of fluids which involves fluid loss into the small intestine and fluid reabsorption from the colon. In the neonatal calf this “flux” involves the secretion and reabsorption of up to 90 litres of fluid per day. When an animal presents at our clinics with diarrhea it means that something has happened to disrupt this cycle. Either 1) Fluid loss in the small intestine is greater than fluid reabsorption in the colon, OR 2) Fluid reabsorption in the colon is less than fluid loss in the small intestine.

II. CLASSIFICATION OF FLUID LOSS?
Neonatal calf diarrhoea can either be classified as 1) Hypersecretory or 2) malabsorptive based on aetiology.
   As the name suggests, hypersecretory diarrhoea arises due to increased secretion of fluid from gut cells. In this case fluid secretion is greater than reabsorption. Hypersecretory diarrhoeas are characterized by bicarbonate, potassium, sodium and water loss into the gut. hypersecretory diarrhoeas are typically seen in cases of enterotoxigenic E. coli infections.
   In contrast, malabsorptive diarrhoeas are associated with damage to the lining of the intestine. Loss of intestinal integrity reduces the ability of the gut to absorb food. Undigested food in the colon results in a hyperosmotic environment which draws fluid into the colon. Malabsorptive diarrhoeas are often foul smelling due to secondary fermentation that takes place in the colon. Malabsorptive diarrhoeas are usually associated with rota virus, corona virus or Cryptosporidium infections.
   Clinically, hypersecretory or malabsorptive diarrhoeas can be differentiated by testing the pH of the faeces. Hypersecretory diarrhoeas have an alkaline pH (> 7) while malabsorptive diarrhoeas typically
have an acid pH (< 7). This classification may have implications in terms of therapy. Some authors have argued that only malabsorptive scours require antimicrobial therapy.

III. CAUSATIVE ORGANISMS

Table 1.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Age (days)</th>
<th>Incidence (UK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>&lt; 5 days</td>
<td>5%</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>5 to 15 days</td>
<td>46%</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>5 to 21 days</td>
<td>11%</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>5 to 35 days</td>
<td>24%</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>5 to 42 days</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>7%</td>
</tr>
</tbody>
</table>

Table 1 summarizes the most common organisms associated with calf scours in the United Kingdom and the incidence and age predilection. It is critical to recognize that the presence of the organism does not necessarily equate to disease. “Pathogens” may be present in healthy and diseased animals. Furthermore many organisms are shed intermittently and so may not be consistently isolated from infected animals. Serological screening of adult animals suggests that almost all cattle have been exposed to these pathogens at some point during infection. Many scour outbreaks may also come about due to a mixed infection associated with 2 or 3 pathogens.

What turns a “normal” often commensal gut inhabitant into a killer?

1. **Poor host immunity**: This normally arises due to inadequate colostrum intake.
2. **Overwhelming challenge**: This arises due to poor hygiene and housing.
3. **Trigger factors**: Stress associated with poor feeding practices or overcrowding.

IV. WHAT ARE THE CONSEQUENCES OF CALF SCOURS?

A. Dehydration
B. Acidosis
C. Hypoglycemia
A. Dehydration

Table 2.

<table>
<thead>
<tr>
<th>Upper eyelid pinch</th>
<th>Mild 4-6%</th>
<th>Moderate 7-9%</th>
<th>Severe &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Globe recession</td>
<td>1-2 sec</td>
<td>3-4 sec</td>
<td>&gt;4 sec</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>None</td>
<td>1-2mm</td>
<td>2-4mm</td>
</tr>
<tr>
<td>Extremities</td>
<td>moist,warm,pink</td>
<td>tacky,warm,pale</td>
<td>dry,cool,pale</td>
</tr>
<tr>
<td>Demeanor</td>
<td>warm</td>
<td>cool</td>
<td>cold</td>
</tr>
<tr>
<td></td>
<td>standing,bright</td>
<td>sternal,slow</td>
<td>lateral,depressed</td>
</tr>
</tbody>
</table>

Dehydration comes about when fluid loss is greater than fluid intake or fluid reabsorption in the colon. Hydration status can be readily determined by evaluating skin elasticity (pinching the upper eyelid); globe recession and the oral mucosa (Table 2). Less sensitive measures of hydration are the extremities and overall demeanour of the calf. Assessing hydration status is important to determine how much fluid to administer over what period of time.

B. Acidosis

Acidosis arises when there is a build-up of hydrogen ions in the tissues. Clinically, acidotic calves are often depressed and seem “dumb”. Acidosis can be caused by:

1. Loss of bicarbonate in the gut
2. Production of acid in the tissues
3. Production of acid in the colon

1. Loss of Bicarbonate in the Gut

In the healthy calf, bicarbonate (H2CO3) scavenges hydrogen in the gut. The product of bicarbonate and hydrogen is water and carbon dioxide. In cases of hypersecretory diarrhoea, bicarbonate is frequently lost into the small intestine. The net effect is the loss of bicarbonate and build-up of hydrogen.

2. Production of Acid in Tissues

Scouring calves are usually dehydrated and therefore hypovolaemic. Hypovolemia results in reduced blood flow to the peripheral tissues resulting in reduced oxygen delivery to the tissues. Reduced perfusion is therefore associated with an increase in anaerobic respiration resulting in an increase in tissue lactate production. Lactic acid production is associated with a metabolic acidosis at the level of the tissues.

3. Acid Production in the Colon

Lactic acid production in the colon is often associated with maldigestive diarrhoea. In these cases, damage to the gut lining results in milk remaining undigested in the gut. Fermentation of milk and milk products in the colon results in lactic acid production. Furthermore, undigested milk in the gut is hygroscopic increasing fluid loss into the colon and producing foul smelling diarrhoea. Lactic acid produced in the colon is absorbed systemically exacerbating metabolic acidosis.

Acidosis can be determined by considering the Base Deficit. This can be determined clinically using the assessment criteria in Table 3:
Table 3.

<table>
<thead>
<tr>
<th>Clinical Assessment</th>
<th>&lt; 8 days old: Base Deficit (mmol/L)</th>
<th>&gt; 8 days old: Base Deficit (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing, strong suckle</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Standing, weak suckle</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Sternal recumbency</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Lateral recumbency</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

C. Hypoglycaemia
Hypoglycemia is essentially a consequence of maldigestion and malabsorption. However, it may be exacerbated when calves become depressed and recumbent due to dehydration and acidosis. Impaired digestion and absorption of milk is usually associated with damage to the gut lining caused by viruses and protozoa.

V. TREATMENT OF CALF SCOURS
Understanding the aetiology and consequences of neonatal calf diarrhoea allows us to establish rational treatment goals:
1. Correction of dehydration
2. Correction of acidosis
3. Correction of hypoglycemia

When considering fluid administration the first decision is whether dehydration can be corrected with oral fluids or if IV fluids are required. For producers the question is usually “Can I do it myself or do I need to call the vet?” Clinically as a rule of thumb, if the calf is < 8% dehydrated; oral fluids are usually sufficient. If the calf is > 8% dehydrated then intravenous fluids are required. In practical terms producers can assess dehydration by observing the demeanour of the calf. If the calf can stand unassisted, oral fluids are usually sufficient. However if the calf is unable to stand, then IV fluids will be required. It is critical that producers understand that this situation can change very rapidly. It is better to err on the side of caution and elect to do IV fluid replacement sooner rather than later.

A. Oral Fluid Therapy
The goal of oral fluid therapy in a scouring calf is to reverse fluid balance from NET LOSS to NET GAIN.

Oral fluid therapy is considered the most important medical advance of the 20th Century by the World Health Organization.

How to Choose an Oral Fluid Replacement
Commercial oral fluid replacements should be judged based on the following criteria:
1. **Rehydration ability**: Rehydration ability depends on the amount of sodium in the replacement fluid. The WHO recommends 90 mmol/L. However optimum rehydration is usually achieved at 120–130 mmol/L.
2. **Ability to correct acidosis**: The ability to correct acidosis is judged by the presence of bicarbonate or bicarbonate precursors (citrate, acetate and propionate). Bicarbonate is least favoured since this may impair abomasal clot formation. If bicarbonate-rich fluids are used, producers should wait
2–3 hours between replacement fluid administration and milk feeding. Fluids should contain at least 25–30 mmol/L bicarbonate precursors. However the optimum appears to be 80–120 mmol/L. In addition to correcting acidosis, there are several additional benefits to using the bicarbonate precursors acetate and propionate in oral fluids. Acetate and propionate may aid the absorption of sodium in the calf small intestine thereby promoting rehydration. The precursors also do not increase abomasal pH therefore inhibiting overgrowth of Salmonella and E. coli. Bicarbonate precursors also produce energy when metabolized.

3. **Nutritional ability:** Milk is the nutritional gold standard by which all oral rehydration therapies should be judged. Glucose is the energy substrate of choice in most oral rehydration therapy solutions. However, the inclusion of amino acids such as glutamine has recently received research attention. Absorption of sodium to correct hydration depends on glucose, volatile fatty acids (Acetate and propionate) and amino acids such as glycine and glutamine. It is also believed that glutamine may be used preferentially as a source of energy by enterocytes.

**Should We Keep Feeding Milk to Scouring Calves?**
Absolutely! Milk contains more energy than any oral electrolyte solution. Initially scouring calves fed milk will probably scour more especially if it is a malabsorptive diarrhoea. However, as long as we provide sufficient fluids to replace the deficit this should not be a major issue. It is suggested that milk should not be mixed with oral electrolyte solutions since this may interfere with abomasal clot formation. We currently recommend adding the oral electrolyte solution as an “extra” meal while still keeping up with the usually milk feeding schedule.

**Comparison Between Some Commercial Oral Rehydration Therapies**

**Table 4.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Sodium</th>
<th>Bicarbonate</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.H.O.</td>
<td>90 mmol/l</td>
<td>30 mmol/l</td>
<td>111 mmol/l</td>
</tr>
<tr>
<td>Lifeaid Xtra</td>
<td>90 mmol/l</td>
<td>50 mmol/l</td>
<td>175 mmol/l</td>
</tr>
<tr>
<td>Lectade</td>
<td>50 mmol/l</td>
<td>28 mmol/l</td>
<td>160 mmol/l</td>
</tr>
<tr>
<td>Glutalyte</td>
<td>120 mmol/l</td>
<td>80 mmol/l</td>
<td>378 mmol/l</td>
</tr>
</tbody>
</table>

**B. Intravenous Fluid Therapy**

Once the need for intravenous fluid therapy has been determined, replacement fluid volume can be determined using the following equation:

**Replacement Fluid Volume = % Dehydration x Bodyweight (Kg)**

Most commercial intravenous fluid solutions are deficient in bicarbonate. Bicarbonate MUST be added to almost all intravenous fluid solutions to correct the base deficit. Correction of acid-base balance can be achieved using the following equation:

**Bodyweight (kg) x 0.5 (L/Kg) x Base Deficit (mEq/litre)**
Bicarbonate requirements can be determined in the field by examining the demeanour of the calf and applying the visual scoring system illustrated in Table 5. An isotonic 1.3% sodium bicarbonate solution can be prepared by adding 13 g of baking soda to 1 litre of colloid fluid. The amount of this 1.3% sodium bicarbonate solution needed to correct the base deficit determined using the visual scale in Table 5 is represented in Table 6.

Table 5.

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Base deficit (mmol/L)</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual</strong></td>
<td><strong>Descriptive</strong></td>
<td></td>
</tr>
<tr>
<td>Standing, strong suck reflex</td>
<td>0</td>
<td>Oral*</td>
</tr>
<tr>
<td>Standing, weak suck reflex</td>
<td>5</td>
<td>Intravenous*</td>
</tr>
<tr>
<td>Sternal recumbency</td>
<td>10</td>
<td>150</td>
</tr>
<tr>
<td>Lateral recumbency</td>
<td>10</td>
<td>150</td>
</tr>
</tbody>
</table>

* Should contain at least 60 mmol/L of acetate or bicarbonate.
* Total bicarbonate requirement for intravenous fluid therapy, mmol.

Table 6.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Wt.</th>
<th>BD: 5 mmol/L</th>
<th>BD: 10 mmol/L</th>
<th>BD: 15 mmol/L</th>
<th>BD: 20 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>66#</td>
<td>30kg</td>
<td>500 mL</td>
<td>1000 mL</td>
<td>1500 mL</td>
<td>1900 mL</td>
</tr>
<tr>
<td>77#</td>
<td>35kg</td>
<td>500 mL</td>
<td>1100 mL</td>
<td>1600 mL</td>
<td>2300 mL</td>
</tr>
<tr>
<td>88#</td>
<td>40kg</td>
<td>600 mL</td>
<td>1300 mL</td>
<td>1900 mL</td>
<td>2600 mL</td>
</tr>
<tr>
<td>99#</td>
<td>45kg</td>
<td>700 mL</td>
<td>1400 mL</td>
<td>2100 mL</td>
<td>2900 mL</td>
</tr>
<tr>
<td>110#</td>
<td>50kg</td>
<td>800 mL</td>
<td>1600 mL</td>
<td>2400 mL</td>
<td>3200 mL</td>
</tr>
<tr>
<td>121#</td>
<td>55kg</td>
<td>900 mL</td>
<td>1800 mL</td>
<td>2700 mL</td>
<td>3800 mL</td>
</tr>
<tr>
<td>132#</td>
<td>60kg</td>
<td>1000 mL</td>
<td>1900 mL</td>
<td>2900 mL</td>
<td>3800 mL</td>
</tr>
</tbody>
</table>

I.V. fluid administration can be challenging especially on farms. In most cases an indwelling jugular catheter provides satisfactory results. In cases where locating the jugular vein proves challenging, the ear or saphenous veins can offer an accessible alternative.

In the Veterinary Teaching Hospital at Kansas State University our clinicians occasionally use Jamshidi Bone Marrow Biopsy Needles to administer intraosseous fluids to scouring calves. If IV access is a challenge, large volumes of fluids can be given intraosseously. An 18ga, 3.5” (9cm) spinal needle or a 15 or 18 ga Jamshidi needle (reusable) can be driven into the intertrochanteric fossa of the femur to provide a temporary route of shock fluid administration. These are used especially in cases where
jugular catheterization is impractical or too costly. Intraosseous fluid administration is a convenient, cost effective and efficacious alternative to jugular catheterization. Jamshidi needles can be sterilized and reused between patients and can therefore be cheaper than jugular catheterization.

**What About Scour Gels (Psyllium)?**
Recently, psyllium-based “scour gels” have become popular in certain regions. These are thought to enhance abomasal emptying. However, recent studies suggest that psyllium may impair glucose absorption thereby enhancing hypoglycaemia. Our clinic is not recommending the use of “gels” at this time.

**ANTIMICROBIAL THERAPY**
Antimicrobial therapy of scouring calves is controversial. Recently, Constable reviewed antimicrobial use in the treatment of calf diarrhoea (*J Vet Intern Med.* 2004;18:8–17). The salient points of this review pertaining to drugs approved for use against neonatal diarrhoea in the E.U are summarized below. I highly recommend this well written article for anyone who requires further information.

Constable states that calves with diarrhoea usually have small intestine overgrowth with *E. coli* regardless of aetiology. Over 30% of systemically ill calves are reported to have bacteraemia associated with *E. coli*. In most cases this is also accompanied by a failure of passive transfer of immunoglobulins. He suggests that the prevalence of bacteraemia is sufficiently high that systemically ill calves (delayed suckle reflex, > 6% dehydration, weakness, recumbency, depression) should be treated with SYSTEMIC antimicrobials. Antimicrobial selection should emphasize gram -ve activity. Based on this review, the 2 primary reasons for administering antimicrobials to scouring calves are considered to be:

1. Decrease the number of *E. coli* in the small intestine
2. Treat potential *E. coli* bacteraemia

**Evidence Against the Use of Certain Antimicrobial Classes for Scour Treatment**
- **Procaine penicillin** (2–60 mg/kg milk replacer) or potassium penicillin (11 mg/kg milk replacer) increased duration of diarrhoea and decreased growth rate compared with untreated controls (Knodt. *Proc Exp Biol Med.* 1953;82:663–665).
- **Neomycin sulphate** (300 mg PO q 24 h for 1–4 days) tended to increase the proportion of calves developing diarrhoea (99/233) compared with untreated controls (59/174) (P = 0.06) (Shull. *Vet Med Small Anim Clin.* 1978;73:924–930).
- **Neomycin** (25 mg/kg PO q6h), **Ampicillin** (12 mg/kg PO q8h), **tetracycline** (11 mg/kg PO q12h) for 5 days increased occurrence of diarrhoea and decreased glucose absorption (Rollin. *AJVR.* 1986;47:987–991).

**Evidence of Successful Antimicrobial Therapy**
Criteria for measuring success of antimicrobial therapy:

1. Mortality rate
2. Growth rate of survivors
3. Increase/ decrease in severity of diarrhoea
4. Duration of diarrhoea
Oral Antimicrobials Against Naturally Acquired Diarrhoea

- **Neomycin Sulphate** (Dose Unknown) given PO for 2 days did not alter mortality when compared with untreated controls however the duration of diarrhoea was shorter in neomycin treated calves (Osborne. 1959;124: 173–177).
- **Ampicillin (12 mg/kg PO q12h for 3–5 days)** had no effect on mortality rate (26/83 treated and 27/82 untreated calves died (P = 0.83) (Radostits. CVJ. 1975;16:219–227)
- **Apramycin (20 mg/kg PO q24h for 5 days)** significantly decreased mortality rate (10/118; P < 0.001) when compared with untreated controls (36/121). Apramycin also increased growth rate in survivors (Pankhurst. Proc World Vet Congress. 1975:1891–1895).
- **Potentiated Sulphonamide (5 mg/kg PO q24h trimethoprim and 25 mg/kg PO q24h sulfadiazine)** administered for 3–5 days had no effect on the proportion of calves returning to normal fecal consistency (88/101) when compared with an untreated control group (23/31) (P = 0.97) (Daniels. Vet Med Small Anim Pract. 1977;72:93–95).
- **Marbofloxacin (1 mg/kg PO q24h for 3 days)** compared with amoxicillin-clavulanic acid (12 mg/kg PO q12h) produced a significantly faster return to normal faeces (Thomas. Proc XXth World Buiatrics Congress. 1998:337–339).

Oral Antimicrobials Against Experimental Diarrhoea

- **Potentiated Sulphonamide (5 mg/kg PO q24h trimethoprim and 25 mg/kg PO q24h sulfadiazine)** administered 24 hours after experimental *S. enterica* inoculation and continued for 5 days tended to reduce mortality rate in treated calves. However, antimicrobial administration was initiated prior to development of clinical signs. Therefore the applicability of these results to “real-world” situations may be questionable (White. Res Vet Sci. 1981;31:19–26).
- **Amoxicillin trihydrate (10 mg/kg PO q12h for 4 days in the milk replacer)** reduced mortality rate and duration of diarrhoea in calves with experimental *E. coli* diarrhoea. Treatment was initiated immediately after diarrhoea was detected (Palmer. Vet Rec. 1977;100:487–491).
- **Enrofloxacin (5mg/kg PO q24h for 3 days)** significantly decreased mortality rate in calves with experimentally induced enterotoxigenic *E. coli* in calves < 1 day old (Navetat. Proc XXth World Buiatrics Congress; 1998:391–393).

Parenteral Antimicrobials Against Naturally Acquired Diarrhoea

- **Apramycin (20 mg/kg unknown route q24h for 5 days)** significantly decreased mortality rate (10/118; P < 0.001) when compared with untreated controls (36/121). Apramycin injection also increased growth rate in survivors (Pankhurst. Proc World vet Congress; 1975:1891–1895).
- **Potentiated Sulphonamide (5 mg/kg IM q24h trimethoprim and 25 mg/kg PO q24h sulfadiazine for 7 days)** did not significantly increase survival when compared with untreated controls (Buntain. Vet Rec. 1980;107:245–248).
- **Ampicillin (6.6 mg/kg IM q24h) and Ampicillin-Sulbactam (9.9 mg/kg IM q24h)** instituted immediately on detection of diarrhoea reduced mortality rate when compared with untreated controls. Efficacy was increased in the presence of the β-lactamase inhibitor, sulbactam (Grimshaw. Vet Rec. 1987;121:162–166).
Parenteral Antimicrobials Against Experimental Diarrhoea

- **Danofloxacin (1.25 mg/kg IM q24h for 3 days)** decreased the time taken to recover to a normal demeanour and increased weight gain when compared with baquiloprim/ sulphadimidine (10 mg/kg IM q24h for 3 days) and untreated controls in calves with experimental enterotoxigenic *E. coli* (White. *Vet Rec.* 1998;143:273–276).

- Potentiated Sulphonamide (4 mg/kg IM q24h trimethoprim and 20 mg/kg PO q24h sulfadiazine for 5 days) administered 24 hours after experimental *S. enterica* inoculation and continued for 5 days **significantly reduced mortality** rate in treated calves. However, antimicrobial administration was initiated prior to development of significant clinical signs. Therefore the applicability of these results to “real-world” situations may be questionable (White. *Res Vet Sci.* 1981;31:19–26).

Evidence-Based Principles of Antimicrobial Therapy for Calf Scours

1. Diarrhoea accompanied by **systemic illness** (i.e., delayed suckle reflex; > 6% dehydration; weakness; recumbency; depression) should be treated with parenteral antimicrobials with a gram-negative spectrum.

2. Randomized, controlled studies support the parenteral administration of fluoroquinolones (danofloxacin, enrofloxacin, marbofloxacin), aminocyclitols (Apramycin) and synthetic β-lactams (ampicillin, amoxyclillin) to treat bacteraemia in scouring calves.

3. Randomized, controlled studies support the oral administration of amoxicillin, apramycin and fluoroquinolones to treat *E.coli* overgrowth of the small intestine. Of these only amoxicillin and the fluoroquinolones are likely to be absorbed systemically and may be effective against bacteraemia.

4. Published studies do not support the oral administration of potentiated sulfonamides, tetracyclines or neomycin in the treatment of calf scours. Furthermore, the efficacy of parenteral potentiated sulfonamides is questionable due to deficiencies in the study design.

5. Calves with diarrhoea and no systemic illness (normal appetite; no fever) should be monitored and not administered antimicrobials.

What Turns a “Normal” Often Commensal Gut Inhabitant Into a Killer?

1. **Poor host immunity**: This normally arises due to inadequate colostrum intake.

2. **Overwhelming challenge**: This arises due to poor hygiene and housing.

3. **Trigger factors**: Stress associated with poor feeding practices or overcrowding.

Vaccination to Enhance Maternal Antibody Production

Immunization with multivalent rota, corona and *E. coli* K-99 vaccine pre-partum is a common practice in many territories. Evidence to support the efficacy of these vaccines dates back to studies conducted in the early Eighties. However, only 1 relevant, controlled study could be found in a brief review of the published literature. If there are more definitive studies out there, these are either proprietary or they have not been published in Journals that can be accessed on PubMed.

Saif and others (*Infect Immun.* 1983 Sep; 41(3):1118–31) demonstrated passive immunity to bovine rotavirus in newborn calves fed colostrum supplements from immunized cows. Colostrum was collected and pooled from each of five cows in three experimental groups:
- **Group I** cows received **intramuscular** (1 week prior to drying off) and **intramammary** (1 week after drying off) inoculations of **adjuvanted** modified live Ohio Agricultural Research and Development Center rotavirus vaccine;
- **Group II** cows were injected **intramuscularly** with a commercial modified-live rota-coronavirus vaccine at 6 weeks and 3 weeks precalving; and
- **Group III** cows were uninoculated controls.

Pooled colostrum from **Group I** cows had higher (P less than 0.05) enzyme-linked immunosorbent assay (ELISA) immunoglobulin G (IgG1) and virus neutralization (VN) rotavirus antibody titers (ELISA IgG1 = 2,413,682; VN = 360,205) than did colostrum from **Group II** (ELISA IgG1 = 8,192; VN = 4,395) or **Group III** cows (ELISA IgG1 = 5,916; VN = 2,865). **The antibody titers of these last two colostrum pools did not differ (P greater than 0.05).**

Samples of these colostrum pools were fed as daily supplements (percent [vol/vol] in cow’s milk infant formula) to 28 newborn, unsuckled, antibody-seronegative, male Holstein calves. Eight calves received no supplemental colostrum. The calves were orally challenged with virulent bovine rotavirus and monitored daily for diarrhoea and faecal rotavirus shedding.

Diarrhoea and rotavirus shedding occurred in the eight calves fed no supplemental colostrum and persisted longest in this group.

The pooled colost0072um from **group I** cows protected eight of eight calves from both rotavirus diarrhoea and shedding when fed as a 1% supplement.

The pooled colostrum from neither **group II** nor **group III** cows protected 12 other calves against rotavirus diarrhoea or shedding when fed at the same concentration (1%).

Six rotavirus-challenged calves fed 0.1% supplemental colostrum from **group I** cows and two calves fed 10 and 50% supplemental colostrum from control cows displayed partial passive immunity, exemplified by delayed onset and shortened duration of rotavirus-associated diarrhoea and virus shedding.

It is unfortunate that the efficacy of these vaccines against naturally occurring rota virus infections in a clinical setting has not been conclusively demonstrated in the literature. This study also found that pooled colostrum from cows that received the vaccine by IM administration did not protect calves against rotavirus diarrhoea or shedding. This raises a number of questions regarding the cost-effectiveness of vaccination in the face of a scours outbreak. Furthermore, producers must understand that vaccination without ensuring that calves receive adequate colostrum. This is especially important in dairy herds. Furthermore, the timing of vaccination can be problematic in herds where record keeping is deficient.

**What is the Significance of Failure of Passive Transfer of Colostral Immunity?**

Louis Perino determined the significance of failure of passive transfer in beef calves (**Am J Vet Res.** 1995;56(9):1149–54). Failure of passive transfer occurs in 10–30% of beef calves. The incidence is much higher in cases of dystocia. Calves receiving inadequate amounts of colostrum are 3–9 times more likely to develop scours and 5 times more likely to die from scours. Transfer of colostral antibodies is most efficient within 6–8 hours of birth. By 9 hours the efficiency of absorption is decreased by 50%. Perino’s
group found that partial failure of passive transfer has implications throughout the production cycle resulting in lower weaning weights and average daily gain.

**How Can We Reduce Pathogen Load in Production Systems?**
Post calving management is a critical component of calf scour prevention. This requires a rudimentary understanding of the epidemiology of viral scours infection.

In production systems adult cows serve as shedders of scour pathogens. This is the primary source of infection for young calves. Once infected, calves become very efficient multipliers of infection which then spreads to other calves in the herd.

It therefore follows that over the course of the calving season, pathogens readily build up in the environment. This increases the risk of infection in later calves. Pair management (Cow and calf) is a critical component of scours prevention. Dispersing pairs to a less densely populated environment as soon as possible after birth will reduce environmental challenge to newborn calves. It is also critically important to keep sick and high risk (dystocia) calves from healthy calves.

A practical example of a pair management system is the Sandhills Calving System developed by Dr David Smith at the University of Nebraska. This system is based on the system of segregating pregnant cows and newborn calves from sick and high risk calves. The basis of this system is demonstrated in the diagram below courtesy of Dr Mike Sanderson and Kansas State University.

![Diagram of the Sandhills Calving System](image)

Calving commences in pasture 1 with close-up cows moving into the observation pen at night. Sick calves and dystocia cases must be isolated to prevent infection and disease spread. Each week the heavy
cows move to the next pasture and the pairs are left behind. This way, newborn calves are spared the "multiplier" effect of the older calves. There is also reduced build-up of pathogens in the environment.

The Sandhills system has proven to be very effective in reducing mortality due to calf scours in herds in Nebraska. In one example, a 900 cow herd experienced mortality due to calf scours of 6.5–14%. This resulted in an average cost of $3,114/ year. Within 1 year of implementing the Sandhills system the cost was reduced to $128.

**Pain Assessment in Cattle**

Hans Coetzee, BVSc, Cert CHP, PhD, DACVCP
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The 21st century consumer is wealthier but also more detached from production agriculture than any in history. Therefore, animal welfare concerns are becoming an important issue to our clients and customers. We recognize that pain is an inevitable consequence of many routine animal husbandry procedures in farm animals. However, how can we assess if cattle are in pain and if our analgesic interventions are working? In this session we will examine novel approaches to measuring pain and analgesic drug efficacy in cattle. We will discuss a practical sub-anesthetic/ analgesic drug combination you can use to take the edge off the fractious cases you encounter.

Nociception is an inevitable consequence of many routine management procedures in farm animals. Castration is considered one of the most stressful experiences for livestock by the American Veterinary Medical Association (AVMA) and is performed on approximately 15 million calves in the U.S annually. Dehorning and castration are especially significant in terms of animal welfare because preemptive analgesia can be applied in advance of the painful stimulus, thereby preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. The AVMA "supports the use of procedures that reduce or eliminate the pain of dehorning and castrating of cattle" and proposes that "available methods of minimizing pain and stress include application of local anesthesia and the administration of analgesics." In spite of this, a recent survey of 184 bovine veterinarians conducted by our research group found that only 1 in 5 U.S veterinarians use anesthesia or analgesics at the time of castration. One reason for this discrepancy is the lack of objective methodology to quantify the most effective pain mitigation strategies.

It is remarkable that although administration of local anesthesia prior to castration and dehorning is legislated in several European countries there are currently no analgesic drugs specifically approved for pain relief in livestock by the U.S Food and Drug Administration (FDA). FDA Guidance Document 123 for the development of effectiveness data for non-steroidal anti-inflammatory drugs (NSAIDs) states that "validated methods of pain assessment must be used in order for a drug to be indicated for pain relief in the target species." The identification and validation of robust, repeatable pain measurements is therefore fundamental for the development and approval of effective analgesic drug regimens for use in livestock. Research to address our limited knowledge in this area is therefore essential to formulating science-based recommendations.

In practical terms, resistance to requiring injectable analgesia for routine castration and dehorning is largely based on time and logistical issues. However, a recent study evaluating novel methods of analgesia for tail docking in lambs demonstrated that castrating by banding in 1–2 day old lambs required an average of 28 seconds without analgesia and 68 seconds when an injectable local anesthetic
was administered by jet-injector. While the United States has not followed other countries in legislating the use of local anesthesia during castration and dehorning, it is appropriate for the veterinary profession to pursue practical, rapid, and effective methods for the relief of pain related to these procedures. The authors are aware of practicing veterinarians that have adopted local anesthesia regimens for these procedures.

**CANDIDATE METHODS TO ASSESS PAIN ASSOCIATED WITH CASTRATION**

The literature pertaining to behavioral response associated with castration has been summarized in an excellent review by Stafford and Mellor (2005). The salient points pertaining to this discussion are summarized below.

**BEHAVIOR**

Assessment of individual animal behavioral changes in response to pain is highly subjective. Escape behaviors demonstrated at castration but not seen afterwards may reflect a pain response or a desire to escape confinement. Studies have reported that surgically castrated calves struggle and kick during the operation but calves castrated with rubber rings are quieter. Macauley and others reported that calves castrated surgically moved around much less than control calves or calves castrated using a Burdizzo. Two days following castration, the surgical and Burdizzo castrated calves were observed to be less active than control calves. Robertson and others found that rubber-ring, Burdizzo and surgical castration caused significant behavioral responses indicative of pain during the first 3 hours after castration. Fisher and others reported that 14 month old bulls castrated surgically stamped their hind feet, swished their tails and grazed less in the afternoon following castration than control bulls and bulls castrated using bands. Behaviors indicative of a painful sensation such as turning the head towards the hindquarters, alternate lifting of the hindlegs, abnormal postures and slow movement of the tail has been reported weeks after rubber-ring castration. The relative level of pain associated with behaviors seen after castration has not been quantified. The characteristics of emotional states such as being fearful, anxious or happy; and other subjective states such as pain sensation and perception are such that they can never be precisely and accurately measured.

**PRODUCTION PARAMETERS**

Production parameters are often too imprecise to reflect the pain experienced by animals following castration. Furthermore, weight gain following castration may be negatively influenced by a decrease in testosterone following removal of the testes. However, assessment of production parameters is critical if animal well-being research is to have relevance to livestock producers. These assessments may take the form of a cost-benefit analysis or a measure of animal performance. In some studies, Burdizzo or surgical castration had no effect on average daily gain (ADG) over a three month period following castration. The ADG of 7 week-old calves during the 5 weeks following castration using rubber rings, clamp or surgery have been reported to be lower than non-castrated calves but similar between the different castration methods. Rubber ring and surgical castration were reported to cause a decrease in ADG of 50% and 70% respectively in cattle aged 8 to 9 months. When 8, 9 and 14 month old cattle were castrated surgically or using latex bands, cattle castrated later had poorer growth rates than those
castrated at weaning. Cattle castrated with latex bands also had lower growth rates than those castrated surgically during the following 4–8 weeks. In a study conducted by Oklahoma State University, 162 bull calves were used to determine the effects of latex banding of the scrotum or surgical castration on growth rate. Bulls that were banded at weaning gained less weight than bulls that were banded or surgically castrated at 2 to 3 mo of age. In a second study, 368 bull calves were used in two separate experiments to examine the effect of method of castration on receiving health and performance. In the first experiment latex banding intact males shortly after arrival was found to decrease daily gain by 19% compared with purchasing steers, and by 14.9% compared with surgically castrating intact males shortly after arrival. In the second experiment purchased, castrated males gained 0.58 lbs more and consumed 1.26 lbs more feed per day than intact males surgically castrated shortly after arrival.

CORTISOL RESPONSE

Several studies have evaluated acute cortisol response as a method to determine the extent and duration of distress associated with castration in cattle. Studies reviewed by Stafford and Mellor indicate that surgical and latex band castrations, especially when performed in older cattle, appear to elicit higher plasma cortisol responses that remain above pre-treatment levels for longer. Peak cortisol concentration following surgical castration occurs within the first 30 minutes after castration and range from 45 nmol/L following rubber ring castration to 129 nmol/L following surgical castration. The duration of plasma cortisol response above pre-treatment levels typically ranges from 60 minutes following Burdizzo castration to 180 minutes following surgical castration. Fisher and others reported that plasma cortisol response was significantly reduced during the first 90 minutes following surgical or Burdizzo castration in calves when the lidocaine was administered prior to the procedure. Lidocaine is a commonly used local anesthesia that has a fast onset of action of 10–15 minutes, and an intermediate duration of action of 60–120 minutes. Based on these data, increases in plasma cortisol are believed to reflect pain experienced as a result of castration.

Cortisol has been widely used as a measurement of distress since its response magnitude, as indicated by peak height, response duration and/or integrated response usually accords with the predicted noxiousness of different procedures. At each end of the cortisol response range, however, interpretation is less straightforward. At the lower end, for example, studies have shown that tail docking with a ring and tail docking with a docking iron cause similar cortisol responses to control handling in older lambs. At the upper end of the range, there are several examples where cortisol responses do not increase proportionally to the severity of different treatments as might be expected. This may suggest a “ceiling effect” on plasma cortisol responses. Other studies have shown that plasma cortisol concentrations following surgical castrations vary greatly between animals. Based on these data, it has been hypothesized that low responses may be due to individuals having high pain thresholds. Variations may also come about due to differences in the way in which a particular castration method is performed by different operators. These data suggest that plasma cortisol levels may not always accurately reflect the extent of the pain response in animals.
**SUBSTANCE P**

Substance P is an 11-amino acid prototypic neuropeptide that regulates the excitability of dorsal horn nocireceptive neurons and is present in areas of the neuroaxis involved in the integration of pain, stress, and anxiety. Studies have shown that plasma SP levels are up to 27-fold greater in human patients with soft tissue injury than healthy controls. Our research group recently conducted a study to evaluate plasma substance P (SP) and cortisol response following castration. Calves were acclimated for 5 days prior to random assignment based on scrotal circumference to a castration or uncastrated control group. Blood samples were collected at -24, -12, and 0 hours pre-castration and 3, 10, 20, 30, 45, 60, 90, 120, 150, 180, and 240 minutes post-castration. Vocalization and attitude scores were determined at the time of castration or simulated castration. Plasma SP and cortisol were determined using competitive and chemiluminescent enzyme immunoassay, respectively. Data were analyzed by repeated measures analysis using a Mixed Effects model allowing for unequal variances. No significant difference in plasma cortisol response between castrated and uncastrated calves was observed over time (p = 0.644). In contrast, mean plasma SP concentrations were significantly higher in castrated calves compared to uncastrated controls over the course of the study (p = 0.042). Cortisol responses over time in calves with vocalization scores of 0 were not significantly different from calves with vocalization scores of 3 (p = 0.17). However, calves with vocalization scores of 3 had significantly higher SP levels when compared to calves with scores of 0 (p = 0.033). These findings contradict previous reports that show an increase in plasma cortisol relative to pain post-castration. Significant increases in plasma SP concentration post-castration suggest that this measurement may be associated with nociception; however, further investigation is necessary.

**ACCELEROMETERS**

Accelerometers have been used in other species to detect lameness and remotely monitor level of animal activity. Our research group has utilized video observations to determine the accuracy of accelerometers to measure behavior changes in cattle and to determine differences in beef bull behavior post-castration. Holstein calves and 12 healthy beef bulls had two-dimensional accelerometers placed on three animals and data was logged simultaneous to video recording of animal behavior. The subsequent data set was used to generate and validate a predictive model to classify animal posture (standing or lying) and type of activity (standing in place, walking, eating, getting up, lying awake, or lying sleeping). The algorithms developed were used to conduct a prospective trial to determine differences in bull behavior in the first 24 hours post-castration (N = 6) compared to both control animals (non-castrated) (N = 6) and pre-castration readings from the same bulls. Based on the analysis of the 2-D accelerometer signal, posture can be classified with a high degree of accuracy (98.3%) and the specific activity can be estimated with a reasonably low misclassification rate (23.5%). Employing the system to compare behavior post-castration revealed that castrated calves spent a larger amount of time standing (79.3%) compared to either pre-castration readings (51.2%) or control calves after castration (64.3%). Animals also spent a lower percentage of the time eating in the post-castration phase. The 2-D accelerometers provided accurate classification of animal posture and reasonable classification of animal activity. Collected data allowed quantification of behavioral
differences between animals after a surgical procedure and provides a valuable tool to compare research with behavioral endpoints.

**RADAR SPEED CAMERAS**
Burrows and Dillon (1997) and Fell *et al.* (1999) used radar speed cameras to measure the speed of cattle exiting a squeeze chute. Cattle with faster exit speeds had lower weight gains, more sickness, and more dark cutting meat. The major problem with chute exit speed as a means to determine pain is that it doesn’t work well for highly acclimated, very tame animals such as dairy cattle. There are also certain breeds such as *Bos indicus* breeds that are more prone to demonstrate rapid chute exit speeds when compared with *Bos taurus* breeds.
Pain Management in Cattle
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It has been suggested that a surgical stimulus such as castration in calves is so brief that little difference can be observed or measured between animals having or not having local anesthetic applied.\textsuperscript{41} However, alleviating pain associated with surgical castration by administration of local anesthesia increased weight gain in cattle for 35 days following castration.\textsuperscript{29} This suggests that alleviating acute pain at the time of castration may have economic benefit.\textsuperscript{11} Ketoprofen, a NSAID analgesic not approved for use in cattle in the U.S., has been shown to reduce acute plasma cortisol response in cattle following administration at the time of castration.\textsuperscript{26-28} Giving both a local anesthetic and intravenous ketoprofen before surgery-cut castration was found to virtually abolish the post-surgery cortisol response.\textsuperscript{27,28} Ketoprofen given alone was also found to reduce the plasma cortisol response to Burdizzo castration more effectively than a local anesthetic or an epidural.\textsuperscript{28} Similar studies examining NSAIDs that are approved for use in food-producing animals in the USA have not been conducted. Furthermore, all these studies examining the efficacy of analgesic drugs in farm animals fail to report associated plasma drug concentrations essential for designing efficacious analgesic regimens. Some of the parameters described above may be useful to allow us to determine the efficacy of analgesics in food animals.

Our research group recently conducted a study to examine the effect of oral aspirin and intravenous sodium salicylate on acute plasma cortisol response following surgical castration.\textsuperscript{33} Twenty bulls, randomly assigned to the following groups; 1) uncastrated, untreated controls, 2) castrated, untreated controls, 3) 50mg/kg sodium salicylate IV pre-castration and 4) 50mg/kg aspirin (acetylsalicylic acid) per os pre-castration, were blood sampled at 3, 10, 20, 30, 40, 50 minutes and 1, 1.5, 2, 4, 6, 8, 10 and 12 hours post-castration. Samples were analyzed by competitive chemiluminescent immunoassay and fluorescence polarization immunoassay for cortisol and salicylate respectively. Data were analyzed using noncompartmental analysis, a simple cosine model, ANOVA and t-tests. Intravenous salicylate Vd\textsubscript{ss} was 0.18 L/kg, Cl\textsubscript{b} was 3.36 mL/min/kg and T\textsubscript{1/2} was 0.63 hours. Plasma salicylate concentrations above 25 µg/mL coincided with significant attenuation in peak cortisol concentrations (p = 0.029). Peak salicylate concentrations following oral aspirin administration was less than 10 µg/mL and failed to attenuate cortisol response. Once salicylate concentrations decreased below 5 µg/mL, cortisol response in the castrated groups were significantly higher than uncastrated controls (p = 0.018). To our knowledge this is the first study relating plasma analgesic drug concentrations directly to mitigation of plasma cortisol response post-castration. These findings have important implications for designing effective analgesic regimens to alleviate the stress response associated with painful routine animal husbandry procedures.

A protocol for use of IM butorphanol/xylazine/ketamine (BXK) was presented by Dr. Matt Miesner, with credit given to Dr. Eric Abrahamsen, at the 2007 Kansas State University June Conference.\textsuperscript{42} The regimen consists of butorphanol (0.01–0.025 mg/kg) + xylazine (0.02–0.05 mg/kg) + ketamine (0.04–0.1 mg/kg). Dr. Miesner noted that for a 450 kg animal, 5 mg butorphanol, 10 mg xylazine, and 20 mg ketamine would constitute the low end of the dosing range. \textbf{Note that the calculation should involve 2x}
Meloxicam

Meloxicam is a NSAID of the oxicam class that is approved in the European Union for adjunctive therapy of acute respiratory disease; diarrhea and acute mastitis when administered at 0.5 mg/kg IV or SC. Meloxicam is considered to bind preferentially to cyclooxygenase-2 (COX-2) inhibiting prostaglandin synthesis although definitive evidence of COX-selectivity in calves is deficient in the published literature. Heinrich et al. (2009) demonstrated that 0.5 mg/kg meloxicam IM combined with a cornual nerve block reduced serum cortisol response for 6 hours in 6–12 wk old calves compared with calves receiving only local anesthesia prior to cautery dehorning. Furthermore, calves receiving meloxicam had lower heart rates and respiratory rates than placebo treated control calves over 24 hours post-dehorning. Stewart et al. (2009) found that meloxicam administered IV at 0.5 mg/kg mitigated the onset of pain responses associated with hot-iron dehorning in 33 ± 3 day old calves compared with administration of a cornual nerve block alone as measured by heart rate variability and eye temperature. These findings indicate that administration of meloxicam at 0.5 mg/kg IV or IM decreases physiological responses that may be linked to pain and distress associated with cautery dehorning in preweaning calves.

The purpose of this study was to investigate the pharmacokinetics and oral bioavailability of meloxicam in ruminant calves. Six Holstein calves (145–170 kg) received either meloxicam IV at 0.5 mg/kg or oral meloxicam at 1 mg/kg in a randomized cross-over design with a 10-day washout period. Plasma samples collected up to 96 hours post-administration were analyzed by LC-MS followed by noncompartmental pharmacokinetic analysis. A mean peak plasma concentration (Cmax) of 3.10 ug/mL (Range: 2.64–3.79 ug/mL) was recorded at 11.64 hours (Range: 10–12 hours) with a half-life (t½ λz) of 27.54 hours (Range: 19.97–43.29 hours) after oral meloxicam administration. The bioavailability (F) of oral meloxicam corrected for dose was 1.00 (Range: 0.64–1.66). These findings indicate that oral meloxicam administration could be an effective and convenient means of providing long-lasting analgesia to ruminant calves.
When a drug is approved by the federal government in Canada for use in food animals, there are label directions for withholding the animal from slaughter and other products (e.g., milk, eggs) from sale to ensure that unsafe drug residues do not enter the human food supply. These withholding periods are established using stringent scientific studies that typically take several years and several million dollars to complete before a drug can be approved. It is therefore critical that livestock producers use these approved products whenever possible and observe these validated withhold times in order to maintain consumer confidence in livestock production and food of animal origin.

Extra-label use of a drug (ELDU) is administering a drug in a manner not specified on its label (e.g., giving a higher dose, giving it more often than directed, giving it to a different type of animal than what it was approved for). ELDU must only be done by direction of a licensed veterinarian, and it is the responsibility of the prescribing veterinarian to ensure that meat or other food products from treated animals do not enter the food supply with unsafe residues. Practicing veterinarians do not always have the necessary information in order to determine safe withdrawal periods for ELDU. To help, the United States and Canada have each developed services that provide recommendations to veterinarians when they must use drugs in an extralabel manner in order to practice good veterinary medicine. The services are cooperative but separate, as there are distinct differences in regulations between the two countries. In Canada, veterinarians can contact the Canadian gFARAD (global Food Animal Residue Avoidance
Databank) through our website (www.cgfarad.usask.ca). There is no charge for our services as we are funded by the commodity groups and the Canadian veterinary pharmaceutical industry.

When choosing drug therapy, Canadian veterinarians must follow a 3-step decision process: 1) They first must choose an approved veterinary product and administer it according to its label directions. 2) If such a situation does not exist, then Canadian veterinarians may choose to use an approved veterinary product in an extralabel manner. 3) Only if there is not a suitable veterinary product available may Canadian veterinarians then choose to use an approved human drug in an animal.

Meloxicam is an approved injectable product (Metacam) for use in calves in Canada. Its label directions are quite specific: “As an aid in improving appetite and weight gains when administered at the onset of diarrhoea, in combination with oral rehydration therapy, in calves over one week of age. For relief of pain following de-budding of horn buds in calves less than 3 months of age.” Therefore use of the drug for the relief of pain from castration falls under the 2nd step of the decision process and is supported as an effective and humane practice from our research studies. In the United States, Metacam is not available in an approved product for cattle, but there are injectable and oral formulations for dogs and cats. In the United States, the 2nd step of the decision process for veterinarians is to choose to use an approved veterinary product in an extralabel manner OR an approved human drug. This is the basis of our work with using human-approved oral meloxicam tablets in calves to relieve the pain of castration.

It is significant that, unlike their counterparts in the United States, Canadian producers have access to an approved formulation of meloxicam with an established safety and residue profile in cattle and therefore do not have to resort to ELDU to provide pain relief at the time of dehorning and castration. 20 days is the approved withdrawal time for the Canadian Metacam injectable product when it is administered according to its label directions. In Canada, it is not appropriate for veterinarians to prescribe human-approved meloxicam tablets to calves when there is an approved cattle product. If there is a compelling reason that the Metacam injectable formulation cannot be used in a specific situation, then prescribing veterinarians should contact the CgFARAD for withdrawal recommendations when using either the small animal Metacam formulations or the human-approved tablets.

Currently the only NSAID approved for use in cattle in the United States is flunixin meglumine. The plasma elimination half-life of flunixin is reported to be 3–8 hours therefore requiring once daily administration. Although this drug class is recognized as having analgesic properties, flunixin is only indicated for control of fever associated with respiratory disease or mastitis, and fever and inflammation associated with endotoxemia, rather than for control of pain. Studies demonstrating the analgesic effects of flunixin at the approved dose of 2.2 mg/kg are deficient in the published literature. Use of flunixin meglumine is further complicated by the requirement for intravenous administration which is more stressful on the animal and involves more skill and training on the part of the operator. Several reports have suggested that the IM administration of flunixin may result in significant myonecrosis and tissue residues.

**Gabapentin**

Gabapentin is a γ-aminobutyric acid (GABA) analogue indicated for treatment of neuropathic pain. This study determined the pharmacokinetics of oral gabapentin alone or in combination with meloxicam in
ruminant calves. Gabapentin capsules at 10 mg/kg PO or gabapentin powder (from capsules) and meloxicam tablets at 15 mg/kg and 0.5 mg/kg PO, respectively was administered to six beef calves. Plasma drug concentrations were determined over 48 h post-administration by liquid chromatography/mass spectrometry followed by non-compartmental pharmacokinetic analysis. The mean (±SD) Cmax, Tmax and elimination half-life (t½ λz) for gabapentin (10 mg/kg) alone was 2.97 ± 0.40 μg/mL, 9.33 ± 2.73 h and 11.02 ± 3.68 h, respectively. The mean (±SD) Cmax, tmax and t½ λz for gabapentin (15 mg/kg) co-administered with meloxicam was 3.57 ± 1.04 μg/mL, 7.33 ± 1.63 h and 8.12 ± 2.11 h, respectively. The mean (±SD) Cmax, Tmax and t½ λz for meloxicam was 2.11 ± 0.19 μg/mL, 11.67 ± 3.44 h and 20.47 ± 9.22 h, respectively. Plasma gabapentin concentrations > 2 μg/mL were maintained for up to 15 h and meloxicam concentrations > 0.2 μg/mL for up to 48 h. The pharmacokinetic profile of oral gabapentin and meloxicam supports clinical evaluation of these compounds for management of neuropathic pain in cattle.

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Economics of Pain Management
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Production parameters are often too imprecise to reflect the pain experienced by animals following castration (Stafford, Mellor, 2005). Furthermore, weight gain following castration may be negatively influenced by a decrease in testosterone following removal of the testes (King et al. 1991). However, assessment of production parameters is critical if animal well-being research is to have relevance to livestock producers. In studies reviewed by Stafford and Mellor (2005), Burdizzo or surgical castration were found to have no effect on average daily gain (ADG) over a three month period following castration (Knight et al. 1999; King et al. 1991). However, the ADG of 7 week-old calves during the 5 weeks following castration using rubber rings, clamp or surgery was found to be lower than non-castrated calves but similar between the different castration methods (King et al. 1991). Rubber ring and surgical castration were reported to cause a decrease in ADG of 50% and 70% respectively in cattle aged 8 to 9 months (ZoBell et al. 1993). When 8, 9 and 14 month old cattle were castrated surgically or using latex bands, cattle castrated later had poorer growth rates than those castrated at weaning. Cattle castrated with latex bands also had lower growth rates than those castrated surgically during the following 4–8 weeks (Fisher et al. 2001; Knight et al. 1999).

In a study conducted by Oklahoma State University, 162 bull calves were used to determine the effects of latex banding of the scrotum or surgical castration on growth rate. Bulls that were banded at weaning gained less weight than bulls that were banded or surgically castrated at 2 to 3 months of age (Lents et al. 2001). In a second study, 368 bull calves were used in two separate experiments to examine the effect of method of castration on receiving health and performance. In the first experiment latex banding intact males shortly after arrival was found to decrease daily gain by 19% compared with purchasing steers, and by 14.9% compared with surgically castrating intact males shortly after arrival. In the second experiment purchased, castrated males gained 0.58 lbs more and consumed 1.26 lbs more feed per day than intact males surgically castrated shortly after arrival (Berry et al. 2001).

LOCAL ANESTHESIA
Several studies have evaluated the effect of local anesthetic administration prior to castration on feed intake, average daily weight gain and inflammatory mediators. In most cases the results of these studies have not shown a significant difference in performance between treated and control calves (Fisher et al. 1996; Ting et al. 2003a; Ting et al. 2003b).

SODIUM SALICYLATE
Salicylate is more soluble than aspirin and may offer a convenient and cost-effective means of providing free-choice access to a NSAID in drinking water. Baldridge et al. (2010) found that calves receiving 2.5 to 5 mg sodium salicylate/mL of water beginning 72 hours prior to concurrent surgical castration and
dehorning and continuing for 48 hours after surgery had a higher average daily weight gain for 13 days after castration-dehorning than untreated calves (Figure 1).

**Figure 1.**

ORAL MELOXICAM

Castration in weaned calves is stressful and affects profitability by reducing ADG and increasing susceptibility to disease. This study evaluated the effect of meloxicam, a non-steroidal anti-inflammatory drug (NSAID), on performance and health of calves received as steers compared to bull calves surgically castrated on arrival at the feedlot. British x Continental bulls (n = 145) and steers (n = 113) (BW = 193 to 285 kg) were transported for 12 h in 3 truckloads (d 0), weighed, and randomly assigned to receive either lactose placebo (CONT; 1 mg/kg) or meloxicam (MEL; 1 mg/kg) suspended in water and administered per os, 24 h prior to castration. On d 1, bulls were surgically castrated (CAST) and steers were processed without castration (STR). Combinations of CONT/MEL and CAST/STR were allocated to 24 pens (6 pens per treatment) of 8–14 calves each. Pen was the experimental unit. Plasma meloxicam concentrations at the time of castration (d 1) were determined by HPLC-mass spectroscopy. Pen-level ADG, DMI, and G:F were estimated using BW obtained on d 0, d 14, and d 28 and weigh-back of feed. Individual animals were classified as sick based on a depression score of ≥ 2 on a 5-point scale and a rectal temperature of ≥ 39.78°C. On d 0, 1, and 14, calf chute temperament was evaluated using a 4-point scale. Data were analyzed using generalized linear mixed models and survival curve analyses. Castration reduced pen ADG (P < 0.001) and G:F (P < 0.001) from d1 to d14, yet no effects were apparent by d 28. For all treatment groups, DMI increased with days on feed (P < 0.0001) but was less in CAST compared to STR calves (P < 0.016) throughout the study. From d 14 to 28, ADG increased in CAST but not STR calves, and G:F decreased in STR but not CAST calves. In CAST calves only, MEL treatment reduced the pen-level first pull rate (P = 0.04) and reduced bovine respiratory disease (BRD) morbidity
rate (P = 0.03) (Figure 2). The frequency of chute escape behavior was greater on arrival and at castration in CAST vs STR calves (P < 0.01) but not different at d 14 (P = 0.22). Mean MEL concentrations at castration were no different between treated STR and CAST calves (P = 0.70). MEL administration prior to castration in post-weaning calves reduced the incidence of respiratory disease at the feedlot. These findings have implications for developing NSAID protocols for use in calves at castration with respect to addressing both animal health and welfare concerns.

Figure 2.

a-b: P < 0.05

SEDATIVE-ANALGESICS

Faulkner et al. (1992) investigated the health and performance effects of intravenous butorphanol (0.07 mg/kg) and xylazine (0.02 mg/kg) co-administration to weanling bulls at the time of castration. Co-administration of xylazine and butorphanol resulted in reduced chute activity and clinical sedation characterized by muscle relaxation and occasional (< 15 to 20%) difficulty in exiting the chute. It is noteworthy that cortisol concentrations immediately post-castration were not evaluated in this study. However, treated calves were found to have significantly higher cortisol concentrations at 3 days post-castration compared with castrated controls. The authors conclude that butorphanol and xylazine did not reduce stress or improve performance.
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Infection Control 101 - Helping to Keep Pets, Clients and Staff Healthy
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In human medicine, the specialty of infection control has been driven forward by global pandemics caused by pathogens such as HIV and methicillin-resistant Staphylococcus aureus (MRSA). Companion animal medicine has been fortunate not to have (yet) had the same kind of high-profile, devastating hospital-associated or zoonotic pathogens emerge on the same scale, but as a result the field of veterinary infection control has been much slower to develop. Over the past few years, the need for better infection control practices, ways to assess infection control and to improve compliance has become clearer. Increasing client awareness of hospital-associated infections (HAIs) and zoonotic infections has played a role, through increasing demand for evidence of good practices. With the ongoing advancement of veterinary medicine, including surgical and chemotherapeutic modalities, companion animals are living longer and with diseases that only a few years ago would have been fatal. However, these patients are living in a compromised immune state and are at a higher risk of infection than ever before. Larger veterinary hospitals are becoming more common and create greater opportunities for pathogen transmission. Another important driving force for improved infection control is the ongoing pandemic of antimicrobial-resistant bacteria, with the astounding emergence of some highly resistant pathogens, such as methicillin-resistant S. aureus (MRSA) and S. pseudintermedius (MRSP), and their impact on infection rates in companion animals. For example, the tremendous increase in MRSP infections internationally over the past several years,1 particularly amongst dermatological and surgical patients, has resulted in surging rates of difficult-to-treat infections, sometimes necessitating the use of aggressive measures such as amputation to control some virtually untreatable postoperative infections. It has also been shown in numerous studies that veterinary personnel - whether they work with small companion animals, horses, swine or even cattle - may be at increased risk of colonization with MRSA, making precautions to protect both personnel and patients of great importance.

With regard to companion animals, infection control is arguably of greatest importance in veterinary clinics, which form community hubs where animals and people of all different kinds - and all different levels of health - meet and interact. Hospital-associated infections can have devastating effects on animals (e.g., suffering, death), owners (e.g., anxiety, financial costs), and veterinary clinics (e.g., stress, financial loss, damage to reputation). These infections can occur as both sporadic (endemic) cases and outbreaks. Reported outbreaks of HAIs in veterinary clinics have involved numerous different pathogens, including MRSA, Salmonella, Escherichia coli, Enterococcus spp., Acinetobacter baumannii, Clostridium difficile, Bordetella bronchiseptica, canine herpesvirus, and feline calicivirus.2-7 Results of a recent survey of biosecurity personnel at 38 veterinary teaching hospitals showed that 82% of these facilities reported at least one outbreak of an HAI in the last five years, and 32% had been forced to close areas of the hospital in order to contain the spread of the pathogen.7 While outbreaks receive the most attention, endemic infections likely have a greater impact. Although poorly quantified, there is a baseline infection rate in the animal patients in every veterinary hospital. Zoonotic infections are an additional concern, as these can affect veterinary personnel and owners in addition to patients, and there is increasing recognition of the role of veterinarians, as part of the household healthcare team, in helping to reduce infections in both people and pets. Transmission of HAIs from pets to owners, and from patients to veterinary personnel, has been clearly documented, particularly involving MRSA, Salmonella Typhimurium and dermatophytes (ringworm).7-11

As understanding of the importance of HAIs and infection control practices in veterinary medicine increases, it is clear that quality infection control practices in veterinary clinics are needed. A study by
Murphy et al.,\textsuperscript{12} which investigated environmental disinfection practices, management of infectious patients and antimicrobial use in clean surgical procedures in veterinary clinics, identified that none of the 101 participating clinics had a recognized infection control program. Infection control practices, including hand hygiene, are more likely to be underutilized under these circumstances, and their effectiveness cannot be evaluated without established policies and a formal infection control program, even if the program is very basic.

Every veterinary clinic, regardless of type or size, should have a formal infection control program. Infection control is ultimately involved in almost everything that is done in a clinic, from washing hands between appointments to what people wear, from how and where animals are handled and housed to how garbage is disposed. Even so, setting up a clinic infection control program is not as complicated as it may seem, and everything does not need to be done all at once; in fact, programs should be designed to develop and adapt over time. Start with the basics. Two essential elements to any effective program are an infection control practitioner (ICP) and a written infection control manual.

**Infection Control Practitioner (ICP)**

Though the title sounds quite formal, the clinic ICP is really a fancy name for the “go-to” person when it comes to infection control issues. The key requirement for this position is simply an interest in infection control - specific training and expert knowledge, though advantageous, are not essential and will in many cases come with time, experience and continuing education. The ICP can be a veterinarian, but often an interested technician with good organizational skills is an excellent choice for an ICP as well. The ICP helps to formalize and document protocols, ensures timely review of existing protocols as needed, collects and reviews surveillance data, keeps staff up-to-date on infection control issues in the clinic, and is available to answer (or find the answer to) any infection control-related questions that may arise. The ICP should also oversee proper training of staff with regard to infection control issues and protocols, and all such training should be documented in order to help protect the clinic from liability in the event of an occupationally acquired infection. The list of duties seems long, but on a day-to-day basis the time commitment is actually relatively small. Nonetheless, the ICP plays a vital role in the implementation of an effective infection control program.

**Infection Control Manual**

Wright et al.\textsuperscript{13} found that only 247/797 (31%) small animal practices, and even fewer large animal and equine practices, had written infection control policies. A written infection control manual is physical evidence of the clinic’s commitment to protecting patients, staff and clients through sound infection control practices. From a legal standpoint, it is often said that if it’s not written down, it doesn’t exist, so having clinic policies formalized in written form can help demonstrate due diligence and protect the clinic from litigation, along with documentation of staff training. The manual also serves as a reference for staff members, including new staff who are being trained, and for more senior staff who may need a “refresher,” particularly for protocols that are not used on a frequent basis. This helps to ensure protocols remain consistent over time and that the details do not get worn away as they are passed on from one person to the next. (A staff member may also be more inclined to look up a protocol on their own if they feel that asking someone else might make it look like he/she does not know how to do his/her job.) The infection control manual does not necessarily need to be lengthy. It may start out as simply a collection of preexisting policies, and additional information and protocols can be added over time. Ultimately the more complete the manual is, the more useful it will be. The manual can be printed as a hardcopy (which should be regularly updated), or it can be stored as a “virtual” manual on the clinic computer network (if applicable), but it should be made readily visible and accessible to all clinic personnel, from veterinarians to kennel staff to volunteers, at all times. Furthermore, every staff
member needs to be made aware of the manual and encouraged to use it appropriately - the very best infection control manual will not do anyone any good if it only sits on a shelf collecting dust.

**SELECTED COMPONENTS OF AN INFECTION CONTROL PROGRAM**

Even though a large proportion of clinics still don’t have a formal infection control program, there are likely many things that are done on an informal basis in these facilities that contribute to infection control. Simply formalizing these procedures and writing them down in one place (i.e., the infection control manual) are an excellent start to setting up a program. The following list is by no means exhaustive, but provides some examples of key program components and considerations.

**Hand Hygiene**

Hand hygiene is considered to be the single most important measure for control of HAIs in human healthcare facilities.\(^{14}\) It is a similarly important measure for controlling the spread of pathogens between animal patients within veterinary hospitals, as well as for preventing the spread of zoonotic pathogens from animals to humans and vice versa,\(^{15-17}\) yet until recently hand hygiene has received very little attention in this context. Available reports indicate that hand hygiene compliance among veterinary staff, as for human healthcare workers, is relatively poor. Increasing hand hygiene convenience through the use of alcohol-based hand sanitizers and sound clinic design, as well as education and motivation of veterinary staff to use this simple measure (and others) more effectively could potentially have a significant impact on infection control in veterinary clinics for relatively little cost.

**Personal Protective Equipment (PPE)**

Personal protective equipment, including regular clinic attire, is important for infection control within a clinic as well as for preventing spread of pathogens into the community.\(^{15-17}\) Appropriate routine PPE items (e.g., scrubs, lab coats) should be changed when they become potentially contaminated over time or grossly soiled. Unlike street clothes, these items are generally made from relatively durable, easy-to-clean material to facilitate frequent laundering. Clinic attire must not be worn outside the clinic, as infectious pathogens may be carried on clothing to anywhere the individual may go, including public places and home, where the person may have close contact with other individuals and animals. If PPE cannot be laundered on-site, it should be taken home in a separate bag and placed directly in the washer, and ideally hot-air dried after washing. The importance of both wearing and changing PPE as needed throughout the day and especially removing PPE at the end of the day must be emphasized to all staff.

Policies should also be set for when additional PPE (e.g., gloves, gowns, face and eye protection) needs to be used. Wright *et al.*\(^{13}\) found marked discrepancies in practitioner perceptions of zoonotic disease risk versus use of PPE when examining animals with potentially zoonotic infections. For example, less than 30% of small animal practitioners who were concerned about the diseases wore appropriate PPE when examining animals potentially infected with rabies, gastrointestinal parasites, gastrointestinal bacteria or dermatophytes. Proper training and enforcement of these PPE policies are important for protecting staff and patients.

**Cleaning & Disinfection**

The role of environmental contamination in the spread of pathogens in veterinary clinics is often unclear. Nonetheless, due to the potential for microbes in the environment (particularly on high-contact surfaces) to be picked up directly or indirectly by animals and people, attention to appropriate cleaning and disinfection protocols is highly recommended.\(^{15-18}\) The goal of these protocols is not to sterilize surfaces (i.e., eliminate all microbes), but rather to reduce the environmental burden to a level at which the risk of infection for the majority of animals and people is as low as possible, within reason. Effective disinfection first requires cleaning to remove gross contamination, followed by adequate contact time
with an appropriate disinfectant that is typically then wiped or rinsed off. Selection of an appropriate disinfectant requires consideration of many factors, including spectrum of efficacy, staff safety, convenience, cost, etc. Use of a different disinfectant from that which is used routinely may be warranted under specific conditions (e.g., involvement of very hardy pathogens such as *Clostridium* or canine parvovirus). Whatever product is used, it is essential that manufacturer’s instructions for proper storage, dilution and required contact time are observed - otherwise, misuse of the product may give a false sense of security that disinfection has been achieved when it has not, pose a health risk to staff or potentially damage surfaces/equipment. Murphy *et al.* reported that veterinarians and technicians generally consider environmental cleaning and disinfection important measures, yet 40–60% did not know what products were used in their own clinics for disinfecting areas contaminated with infectious body fluids, nor how to properly prepare the products for use.

**Patient Handling & Housing**

Front office staff, even if they have very limited clinical duties, play a key role in infection control with regard to triage of animals with transmissible diseases before and at arrival to the clinic. A list of syndromes and conditions that should be “red flagged” as potentially infectious should be compiled, and staff trained to inquire about and recognize key clinical signs (e.g., coughing, diarrhea, skin infections) so that such animals can be admitted directly to an exam room or isolation, thus avoiding contact with other patients in and contamination of the reception/waiting area.

Every clinic must have a functional isolation area to house, even temporarily, animals with known or suspected infectious diseases. Many clinics have small, cramped isolation areas that are frequently used for storage most of the time, making them so inconvenient as to discourage proper use. Putting high-risk cases in makeshift “isolation” in other areas of the clinic puts other patients at risk. An effective isolation unit requires an adequate physical space as well as compliance with appropriate protocols.

**Surveillance**

Surveillance is often quite an intimidating component of infection control for most practitioners, but contrary to popular belief it does not require a great deal of time or money on a day-to-day basis, nor an advanced degree in epidemiology or statistics. At a minimum, passive surveillance can (and should) be done in all clinics, as all it requires is for data that already exists (e.g., lab tests, information from client callbacks) to be collected in one place, and for someone to **look** at it to identify any obvious trends. Syndromic surveillance requires collection of only basic clinical data (i.e., no testing costs), and can provide very valuable information for alerting staff to emerging problems. Active surveillance, such as screening animals for a certain pathogen on admission or discharge, is typically unnecessary unless there is a particular concern or an emerging/ongoing outbreak.

**Staff Safety**

Animal bites and scratches can lead to serious infections, and therefore their prevention is considered part of an infection control program. Bites and scratches should never be considered “part of the job,” and can be a serious liability issue when they affect clients or staff. Although in a significant proportion of cases, at least in otherwise healthy individuals, these wounds heal with basic care and time, when complications arise they can be very serious, resulting in short-term consequences (pain, decreased function, time off work) and in some cases can have long-term consequences (e.g., loss of function, permanent scarring, loss of digits/limb). Basic prevention measures are a small price to pay to avoid such results. All bite incidents (and ideally serious scratches that break the skin) should be reported to a designated individual such as the clinic ICP. Staff should be trained to thoroughly wash and properly bandage (if necessary) the wound - this may seem apparent to some, but others (e.g., clients, lay staff) may not realize the importance of immediate wound care. If the wound is to the hands or groin, or over a joint or tendon sheath, there is a higher risk for complications, and the person should be directed to
seek medical attention if pain, heat, swelling or discharge persists beyond a reasonable period. If the person is immunocompromised, he/she should consult a physician regardless. In the case of bites, when the incident is reported the rabies vaccination status of the victim and the offending animal should also be verified, and the potential need for post-exposure prophylaxis evaluated in consultation with public health.

Sharps handling practices are another important infection control and safety consideration in veterinary clinics. Studies have indicated that 64–93% of veterinary personnel have experienced at least one needlestick and sharps injury (NSI) in their career,\textsuperscript{19-23} and in one report 74% of veterinary technicians had experienced a NSI in the last 12 months.\textsuperscript{20} As in human medicine, NSIs in veterinary medicine are likely significantly underreported.\textsuperscript{20,24} Although there are currently very few recognized bloodborne pathogens that can be transmitted between domestic animals and humans, reports of such transmission do exist,\textsuperscript{25,26} and the risks of other potential consequences of NSIs (e.g., trauma, local tissue infection, allergic or inflammatory reactions to drugs or biologics inoculated or injected into the tissues) are the same or potentially higher when working with animals and drugs not intended for use in humans.\textsuperscript{20,22,27} Policies regarding who should handle sharps, avoiding high-risk procedures such as needle recapping, and providing appropriate disposal containers in all areas where sharps are used should be included in the clinic infection control program.

**Infection Control Culture**

One of the biggest obstacles to effective infectious disease control, be it in a human or veterinary medical setting, is achieving compliance with new and established protocols. Infection control practices often seem like an added encumbrance - no one can deny that additional time and effort are required to perform them, and they may be perceived as a hindrance during very busy periods in particular. Add to this the fact that infection control provides only a negative benefit: when it is done well, infections don’t happen, and life carries on seemingly “as it should.” Particularly in the absence of a disease outbreak, or when insufficient surveillance is performed to detect an outbreak, rising endemic disease or pathogen carriage (as is often the case in small primary care facilities), there is little direct motivation for staff to put in the extra effort, and these practices may fall by the wayside. Caught in such an unprepared and unpracticed state, the clinic is then perfectly ripe for an outbreak to occur, after which there is a major push for better infection control - for a time, and then the cycle repeats.

Education is often the first intervention considered to improve compliance, but while important and even essential, improving knowledge alone is often insufficient. Achieving behavioural change can be very challenging because of the many complex and interactive factors that affect human behaviour. The ultimate multimodal intervention is the creation of an infection control culture. There is currently a lack of infection control culture in veterinary clinics and in veterinary medicine in general; this issue must be addressed if sustained improvement in infection control practices is to be achieved. Establishing an infection control culture does not mean infection control topics need to take over clinic communications, be they in written, oral or other forms. The key is to make infection control a pervasive, but not an overwhelming component of all these things, such that it serves as a reminder without interfering with or overpowering other messages. It is also important to realize that establishing such a culture does not happen overnight, especially when starting from scratch. Attempting to effect dramatic changes in multiple behaviours of multiple people all at once will often be met with resistance and ultimately result in exhaustion of the person(s) at the heart of the attempt. Start small. As time passes and more individuals come on board with the ideals and everyday routine of practicing better infection control, the effect will snowball, and other/new staff will more easily accept and incorporate infection control culture into their own. Hopefully the same phenomenon will ultimately take effect across the veterinary field.
CONCLUSION
A chain is only as strong as its weakest link, and the same can be said for any infection control program. In order to be effective, infection control measures need to be practiced by every member of the clinic staff, from owners and veterinarians to kennel staff and volunteers. Veterinarians and senior staff in particular need to serve as examples to other support staff by taking the time to perform hand hygiene and use other infection control measures. Giving staff adequate time to perform hand hygiene, proper cleaning and disinfection, changing of personal protective equipment and other tasks demonstrates the importance that is placed on these practices and thereby contributes to the infection control culture. Several studies have suggested that involvement and support of upper-level management and administration are necessary for effective implementation of hand hygiene protocols in human health care facilities, and it is likely that the same is true in veterinary clinics, for both hand hygiene and other routine infection control measures. Without the support of owners and management, the entire infection control culture is undermined, and the infection control program is bound to fail.

Remember that there is no “recipe” for infection control, nor is there a “one size fits all” program that can be used in all facilities. Infection control programs need to be tailored to a specific clinic, based on physical resources, staff resources, caseload, local and regional infectious disease risks, risk adversity of clients and staff, and overall cost-benefit. However, there are several resources available that can help provide a framework from which to get started. Emphasis on infection control shows a commitment to protecting animals and people from infection, and to offering a higher standard of overall care.

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Pause to Clean Your Paws - Hand Hygiene in Veterinary Clinics
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Hand hygiene is said to be the single most important factor in infection control in hospitals and other healthcare facilities. It is also a key intervention point to help prevent the spread of common zoonotic pathogens, such as methicillin-resistant S. aureus (MRSA) and enteropathogens, between animals and humans. Hand hygiene also has the potential to help decrease the risk of non-zoonotic pathogen transmission between animals in veterinary clinics via the hands of clinic personnel. Recommendations regarding hand hygiene, including when, how and how often it should be performed, appear in guidelines from multiple healthcare-associated organizations,⁴,⁵ as well as some veterinary infectious disease control guidelines.⁴⁻⁶

The goal of hand hygiene in the context of modern healthcare is to reduce or eliminate the transient microflora of the hands asatraumatically as possible and ideally to prevent rebound growth, in order to decrease the likelihood of transfer of pathogenic or opportunistic microbes from the hands to other surfaces or individuals/tissues.⁷,⁸ This may be accomplished by physical removal of the microbes from the skin, or use of antimicrobial compounds that kill or neutralize the microbes. The resident microflora of the skin is more difficult to remove but is also less likely to include pathogens.¹,³ Maintaining the integrity of the skin even after repeated hand hygiene attempts is crucial, as skin damage provides niches for opportunistic pathogens to cause infection, resulting in pain and discomfort as well as increased risk of transmission due to the larger number of pathogenic bacteria present on the skin.³,⁷

Soaps or detergents are primarily emulsifying agents that break up oils to help mechanically remove contamination from the hands via the flushing action of the water.¹,³ Plain soap has no residual activity against microorganisms, but is suitable for use in lower-risk situations (e.g., homes, general public restrooms), whereas use of antibacterial soap is recommended in healthcare settings, and this could be reasonably extended to include veterinary clinics.

Alcohol-based hand sanitizers (AHSs) rely on the action of the alcohol component to rapidly kill microorganisms by denaturing proteins, which is most effective at a concentration of 65–90%. The alcohol then evaporates relatively quickly, but many AHSs also contain other active ingredients (e.g., chlorhexidine, quaternary ammonium compounds, octenidine, triclosan) that remain on the skin and provide some residual disinfectant action.¹ Alcohol-based hand sanitizers are very convenient, because they do not require water (and therefore sinks/plumbing and a drying mechanism); therefore, dispensers are easily placed and used in any point-of-care area. These products have been shown to be more effective than handwashing with soap and water in the presence of jewelry such as rings, under which bacteria may be harboured,⁹ and they are actually less damaging to the skin over time than soap and water.⁷ The main disadvantage of AHSs is that they do not physically remove microorganisms from the skin. There are some microorganisms that are inherently resistant to even the nonspecific killing action of alcohol (e.g., clostridial spores, Cryptosporidium oocysts, certain nonenveloped viruses such as canine parvovirus); therefore, AHSs are (theoretically) ineffective in terms of controlling contamination with these types of pathogens. Significant (i.e., visible) amounts of dirt/debris/discharge are not removed by using AHS, and may protect microorganisms from the action of the active ingredients in these products. If hands are visibly soiled, or if there is suspected contamination with an alcohol-resistant pathogen, it is therefore recommended that soap and water be used instead of a AHS.¹,²,⁶

Another disadvantage of AHS is that the liquid is flammable due to its high alcohol content, which has been an issue in terms of placing AHS dispensers in some public places, and requires precautions for storage of large volumes and cleanup of large-volume spills.
How well hand hygiene is performed when it is attempted is equally important to timing and frequency for hand hygiene to be effective. In order to effectively reduce or kill the transient microflora of the hands, it is generally recommended that soap be applied for a minimum of 10–20 s before rinsing, or for AHS that enough product be applied to cover all surfaces of the hands and then rubbed until dry (which should take approximately 10–20 s as well).\textsuperscript{1,5,6} Areas of the hand most often missed during washing are under the nails, back of fingers, back of the hands and parts of the thumbs.\textsuperscript{3}

Hand hygiene should be used after activities that may result in contamination of the hands, as well as before activities that may result in transmission of the transient flora of the hands to a common surface or another person or animal. Individuals have a relatively easy time remembering to wash their hands when they are visibly soiled, with the possible exception of veterinary personnel working in a situation when their hands are expected (or accepted) to be dirty, such as in a barn environment. Unfortunately, in the majority of human and veterinary healthcare situations, as well as much of everyday life, microbial contaminants on the hands are not accompanied by visible dirt. In healthcare, be it human or veterinary, hand hygiene should ideally be performed before and after every patient contact and after glove removal in situations when gloves are worn for patient (or specimen) contact.\textsuperscript{1,3,6}

As much as possible, hand hygiene should be performed immediately before and after patient contact, in order to minimize the opportunity for contamination of the hands or by the hands of the person in question. This requires hand hygiene stations to be readily available in all patient contact areas, but this has not been a consideration in the design of many veterinary clinics (i.e., clinics that do not have a sink in all exam rooms and wards). In both healthcare and non-healthcare settings alike, hand hygiene should also be performed after any activity that carries a reasonable risk of hand contamination with potentially harmful pathogens, such as contact with feces (e.g., after using the toilet, scooping dog feces, cleaning a cat litter box), soil or any raw meat/animal product.\textsuperscript{10} Hand hygiene should also be performed before any activity that carries an increased risk of transmission of pathogens from the hands to oneself or a highly susceptible individual (e.g., preparing or eating food, handling an infant, close contact with an immunocompromised animal or individual).\textsuperscript{10}

Compliance with hand hygiene protocols is the most challenging component of ensuring efficacy. Numerous studies have investigated hand hygiene compliance in hospitals.\textsuperscript{1,11} In general, compliance is poor (< 50%) among healthcare workers, and physicians tend to have lower compliance with hand hygiene protocols than nurses.\textsuperscript{8,12} Major barriers to compliance in many situations include skin irritation (irritant contact dermatitis), lack of accessibility to hand hygiene stations, time constraints (i.e., too busy), and lack of perceived importance (i.e., that it is generally unimportant or more likely that it is less important than other tasks/procedures, which therefore take precedence over hand hygiene).\textsuperscript{1,13} The impression that use of gloves negates the need for hand hygiene is problematic and has been reported as a barrier to hand hygiene compliance in human healthcare studies.\textsuperscript{8,13,14} Although gloves do provide an additional barrier between the skin of the wearer and the patient and/or objects the wearer may touch, preexisting defects, damage/punctures that may occur during use, and contamination of the hands during glove removal make gloves an imperfect barrier.\textsuperscript{1,15} Since gloves are most often used in situations when there is a need to take additional precautions to prevent contamination of a site with bacteria from the hands, or when heavy contamination of the hands or contamination with a serious infectious pathogen is expected to occur, hand hygiene before and after glove use remains necessary for infection control. Another barrier to hand hygiene compliance is that in some cases people may simply forget to perform hand hygiene;\textsuperscript{1} to prevent this, hand hygiene needs to become an automatic habit for healthcare and veterinary personnel, like covering a sneeze or a cough.

Literature regarding hand hygiene in veterinary healthcare specifically is limited. Traub-Dargatz et al.\textsuperscript{16} examined the effectiveness of traditional handwashing versus AHS following basic physical examination of a horse, and found the AHS to be more effective at reducing bacterial counts on the hands. However, it was pointed out that the hands of veterinary personnel working in equine practice
may become more heavily soiled on a regular basis than personnel working in a small animal or human hospital, which may require handwashing to remove gross contamination, rather than use of AHS alone for hand hygiene. Anderson et al. 17 found that handwashing following contact with infectious cases and between farms had a protective effect against colonization with MRSA in veterinary personnel who work with horses. With regard to hand hygiene compliance, in two studies of companion animal veterinary personnel, self-reported compliance (i.e., always perform hand hygiene between patients) was 42–48%, 18,19 while observed compliance rates in one veterinary teaching hospital were 21–42%.20 In the study by Wright et al. 19 self-reported compliance among large animal and equine practitioners was even lower (<20%). Only slightly more than half of small animal practitioners in the same survey (590/1069) reported always washing their hands before eating, drinking or smoking while at work, and the same was true for less than a third of large animal and equine practitioners. Nakamura et al. 18 reported the most commonly cited reason for not performing hand hygiene among veterinary support staff was being too busy (72%).

Providing better access to hand hygiene stations and supplies is often the first step to improving hand hygiene compliance, as it aids in minimizing the time required to comply with protocols and acts as a visual reminder to perform hand hygiene. Because renovating most facilities to improve the location of sinks for handwashing is usually not feasible, improving access typically involves introducing or changing the location or number of AHS dispensers.1 From an infection control standpoint, sink placement is a critical consideration in the design of new clinics, in order to facilitate hand hygiene as much as possible, particularly in the most common patient contact areas (i.e., exam rooms, treatment rooms, wards).

Convincing people of the importance and utility of hand hygiene in curbing the spread of infectious agents is crucial to achieving compliance.1 The perception that hand hygiene is relatively unimportant is likely more problematic in veterinary medicine compared to human medicine. Because there are fewer diseases that can be transmitted from animal-to-person compared to person-to-person, some veterinary personnel have a relatively cavalier attitude toward contamination of hands/clothing/equipment with animal blood, body fluids and excreta. However, hand hygiene is also a critical means of preventing potential indirect transmission of non-zoonotic pathogens from animal to animal, thus protecting veterinary patients. The potential of a zoonotic pathogen, brought into a clinic by a single person or animal, to spread first through the clinic and then into the community is significant. Examples of this kind of event have occurred,21,22 and many more likely go unreported or simply unrecognized.

Ideally hand hygiene should be something that everyone wants to do, rather than something everyone must be asked to do, but education alone is frequently insufficient to change behaviour. Development of a clinic infection control culture, whereby infection control practices and principles become integrated into the group mentality through ongoing communication, conversation, training and strong support from team leaders/management, is the ultimate means of improving compliance with hand hygiene and other infection control measures.23

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Disease Surveillance in the Veterinary Clinic - What’s in It for Me?
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INTRODUCTION
Surveillance is an important tool for identifying and responding to changes in disease frequency and epidemiology, including outbreaks. It allows for the detection of nosocomial and zoonotic agents and for monitoring disease prevention and control practices. As such, it is an integral component of an infection control program. Surveillance programs have played a critical role in disease prevention and control in the human and food/production animal health sectors. Yet, companion animals have not historically been a part of national or local surveillance efforts, and there is a lack of use of surveillance in the small animal clinical setting. Recent appreciation of the importance of companion animals as sentinels for emerging zoonotic diseases and the utility of surveillance data for studying and responding to changes in the epidemiology of infectious and noninfectious disease has resulted in new initiatives in this field. Significant efforts are being made by companion animal veterinary teaching hospitals and private clinics to incorporate surveillance systems into their infection control programs. A surveillance program does not need to be complicated, expensive, or take an excessive amount of staff time. However, time should be spent ahead of time to ensure the program that is developed meets the needs of the clinic. The following serves to provide program suggestions and highlight areas to address to ensure the program is tailored to meet your needs.

WHAT IS SURVEILLANCE?
Surveillance is a system based on continuous information recording, making it possible to monitor the health status of a given population and the risk factors to which it is exposed, to detect pathological processes as they appear and study their development in time and space with the objective of taking appropriate measures to control them (surveillance = monitoring/data collection + action). This does not mean that data are continually collected on a daily basis, but that the system is permanently in place (and not a limited duration).

WHY DO WE NEED SURVEILLANCE IN CLINICAL PRACTICE?
Hospital-associated infections (HAI) are a well-recognized contributor to illness and death in human hospitals. HAIs are the fourth leading cause of patient death in Canadian human hospitals, accounting for billions of dollars in healthcare costs. Although similar statistics are not available for veterinary medicine, HAIs likely play an equally important role. A recent study reported that 82% of veterinary teaching hospitals documented one or more outbreaks of hospital-acquired infections during the preceding 5 years. Surveillance programs allow for early recognition of nosocomial transmission and outbreaks, as well as provide important information for better understanding and responding to local disease occurrence (e.g., tracking cases of antibiotic-resistant infections, enteric pathogens, reportable pathogens). Surveillance helps to define the typical (baseline) for disease frequency in a given practice, so that changes in this frequency can be accurately interpreted and logical decisions can be made regarding control and prevention methods. In addition, it allows for the evaluation of compliance with infection-control procedures.

A few recently developed national/regional surveillance systems for small animal practices help to illustrate the utility and design of such programs.

   Maps depicting the relative prevalence of tick-borne pathogens, intestinal parasites and
Heartworm are provided for the United States. Data are derived from results of testing performed by IDEXX Laboratories and ANTECH Diagnostics.

2. **CICADA survey (United Kingdom):** [http://uk.cicasurvey.com](http://uk.cicasurvey.com)
   Provided free of charge to registered practices in the UK, CICADA shows up-to-date reported disease trends in companion animals, including recent outbreaks and current hot spots. Data are provided by participating small animal clinics through periodic mandatory web-based surveys.

3. **Disease WatchDog (Australia):** [www.diseasewatchdog.org](http://www.diseasewatchdog.org)
   Disease cases are logged by participating veterinary clinic staff, and cases are then mapped in real time. Cases can be entered by vet clinics either at the time an animal presents to the clinic, or monthly. It is an initiative of Virbac Animal Health.

**How Do We Go About Setting Up a Surveillance System for a Practice?**

To be effective, there are a number of areas that need to be considered when establishing a surveillance system.³

1. **Who will set up and monitor the system?** Ideally, a single person will frequently monitor data to increase the likelihood of recognizing a trend or related cases.
2. **How are cases identified and defined (case definition)?** A case definition must be well thought out and consistently used.
3. **What type of system will be used (see below) and what data will be collected?** A number of factors may play a role in this decision, such as cost, pathogens of interest, what is acceptable to those taking part in data collection and analysis, ability to alter the system to adapt to change (scalable), reliability in detecting disease, speed at which information can be obtained, and number of high-risk cases routinely housed in or seen at a facility.
4. **How often will data be formally analyzed and reported?**
5. **Who will receive reports?**
6. **What are the triggers for initiating further analysis/surveillance or responding with infection control and prevention practices?**
7. **Are there areas that need to be addressed regarding owners’ approval for collection of samples used solely for the purpose of surveillance, and how will results from such tests be provided to clients?**

A working group should be identified to define objectives and address the above areas. The surveillance plan that is developed should be documented in writing and become part of the clinic’s infection control plan.

**Determine the Type of Surveillance That is Indicated/Acceptable**

There are three main types of surveillance: active, passive, and syndromic.

**1.) Active Surveillance**

Active surveillance involves collection of data specifically for infection control purposes (e.g., laboratory samples taken specifically for purpose of surveillance). May elect to only collect from a subset of patients (e.g., high-risk, certain days of the week).

**Example:** Active methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance is used at some large animal clinics (e.g., Ontario Veterinary College), with nasal swabs collected from horses on admission, every 7 days in hospital, and on discharge. Swabs are screened for MRSA using enrichment media. Molecular typing is performed on MRSA-positive isolates. A classification scheme, such as listed below,³ is then utilized to determine the most likely source of positive isolates.

- Community-associated (CA): Detected at admission
• Community onset-hospital associated (CO-HA): Detected at admission from a horse who was admitted to the same hospital within the previous 12 weeks
• Hospital-associated (HA): First sample negative and MRSA detected on subsequent sample
• Indeterminate (IN): First sample positive but taken > 48 hrs after admission

**Advantages:** Ensures all animals of interest are included; data may be available earlier than if relying on passive or syndromic methods (able to identify asymptomatic shedders); data typically high quality.

**Disadvantages:** Expensive; requires staff time to collect samples.

Environmental surveillance (a form of active surveillance) is sometimes used in hospitals. This form of surveillance typically involves culturing the clinic environment. Environmental contamination in veterinary clinics is common. A recent study\(^4\) found zoonotic pathogens could be isolated from common environmental surfaces (table/floor surfaces, equipment) in a large proportion of community veterinary clinics [Clostridium difficile (58%), methicillin-resistant Staphylococcus aureus (9%), methicillin-resistant Staphylococcus pseudintermedius (7%), and Salmonella (2%)]. Given the profound contamination present, the utility of routine culture-based environmental surveillance in the small animal clinic setting is of questionable use. Environmental cultures could be considered in the context of an outbreak investigation, with assistance of relevant experts for proper design and interpretation. Rather, a more general approach to the assessment of cleaning/disinfection through environmental tagging has been proposed.\(^5\) This method involves the placement of a fluorescent dye on locations of interest, followed by UV light visualisation after cleaning should have been completed. Detection of the dye after cleaning suggests areas were missed or inadequately cleaned. Using this method, Weese et al.\(^3\) documented significant differences in the prevalence of successful cleaning by general location (P < 0.0001) and surface type (P < 0.0001), leading to the identification of inadequacies in protocols and practices, which could be remedied. This technique is an efficient, low-cost tool that can be useful in establishing baseline cleaning rates, identifying deficiencies in protocols, and evaluating the effects of interventions and education of personnel.

2.) Passive Surveillance

Passive surveillance involves the use of data that are already available (e.g., medical records, diagnostic laboratory samples submitted for other purposes).

**Example:** Passive surveillance may be used to monitor postoperative surgical site infections (SSIs) by reviewing case records and client communication for surgical patients at discrete time points after the procedure. Standard definitions can be used to classify reports as SSI,\(^6\) such as:

- **Superficial incisional SSI:** Infection occurs within 30 days after the procedure, involves only skin and subcutaneous tissue of the incision, and patient has at least one of the following:
  - Purulent drainage from the superficial incision
  - Organisms isolated from an aseptically obtained culture
  - Superficial incision that is deliberately opened and is culture-positive or not cultured, and patient has at least one of the following signs or symptoms: pain or tenderness, localized swelling, redness, or heat.

*Similar definitions are available for deep incisional and organ/space SSIs.*\(^6\) A standard approach commonly used is to perform 30-day postoperative surveillance with additional investigation 1 year postoperatively for procedures that involved an implant.\(^7\)

**Advantages:** Data have been collected for other means, so are available and possibly minimal effort (although considerable time can be spent cleaning and analyzing these data).

**Disadvantages:** Only as good as the data that are collected for clinical purposes; may not be effective means of detecting problems, particularly if follow-up is not uniform for all cases; potential
biases must be considered (e.g., more apt to culture infections that do not resolve with empirical therapy, thereby overestimating the proportion of multidrug-resistant infections).

Note: SSI surveillance should be considered by clinical practices. A recent prevalence study found that SSIs were the most common human healthcare-associated infection, accounting for 31% of all HAIs among hospitalized patients. Additionally, recent work at a veterinary teaching hospital identified SSIs in 28/946 (3.0%) animals undergoing surgical procedures. Many (21%) SSIs were only identified through active followup and were not in the medical record. SSIs were most common following orthopedic surgeries and procedures with an implant (6.1%). TPLO was associated with greater odds of SSI (OR = 3.2). Methicillin-resistant staphylococci were most commonly identified, with methicillin-resistant Staphylococcus pseudintermedius accounting for 47% of SSIs. These types of findings highlight the utility of a surveillance system, as they provide a benchmark for SSIs and information that should be monitored and addressed with an infection control program.

3.) Syndromic Surveillance
Syndromic surveillance involves detection of readily identifiable syndromes (e.g., coughing, diarrhoea), not specific diseases. Syndromic surveillance is an easy tool for identification of certain high-risk cases and can be applied by veterinary and lay staff. The use of syndromic surveillance for nosocomial illness (e.g., onset of vomiting/diarrhea during hospitalization) may be a simple, effective tool if there is high staff compliance.

Example: A recent report describes the use of syndromic surveillance to identify and halt the nosocomial transmission of canine parainfluenza in a veterinary teaching hospital. Veterinary kennel staff quickly alerted infection control personnel of two fully vaccinated dogs that had recently been hospitalized in the same ward at the clinic and were now presenting with cough and fever. Infection control was able to act quickly, ensuring the presenting cases were placed in isolation and appropriate personal protective equipment (PPE) was used; suspected contacts in the ward were identified and quarantined; appropriate patient testing and followup was performed; and monitoring of hospitalized patients for signs of respiratory disease or fever of unknown origin was increased. Canine parainfluenza infection was diagnosed through identification of seroconversion of all tested dogs. A total of 4 hospital-associated cases were identified (all occurring through first-generation transmission; infectious agent from the index case to the first group of secondary cases) before clinical illness was apparent; no within-hospital second-generation transmission was observed. This example supports the utility of syndromic surveillance with prompt infection control measures as an integral part of an infection control program.

Advantages: Allows for quick, easy characterization; all staff can participate in case identification.

Disadvantages: Broadly defined groups may not permit accurate identification of clusters/outbreaks; many suffer from high false-positive or false-negative identifications.

Note: Syndromic surveillance can be a useful tool to identify higher-risk patients prior to admission (e.g., recent history of coughing, diarrhea, vomiting), so that specific infection control practices can be employed (e.g., admitted directly into isolation or an overflow examination room) to reduce the initial risk of transmission should an infectious pathogen be present.

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**INTRODUCTION**

Pet ownership is common in North America. Studies report that over 50% of Canadian households own cats or dogs, with other companion species also reported.\(^1\) Although pet ownership has many established health benefits, pets can also be a source of disease for pet owners. The disease risks associated with pet ownership are believed to be highest amongst young children, the elderly, pregnant women, and those with an impaired or weakened immune system (immunocompromised, immunodeficient). Estimates suggest the proportion of individuals with some degree of immunodeficiency is high. As such, animals are frequently a part of households with one or more individuals who have some degree of immunodeficiency. Pet ownership and contact recommendations are established for high-risk groups and can reduce the risk of pet-associated disease. Veterinary staff are in a key position to provide these recommendations to clients and promote safe pet ownership practices. Encouraging and safeguarding client disclosure of immunocompromising conditions is critical for effectively providing this service.

**HEALTH BENEFITS OF ANIMAL OWNERSHIP**

The mental and physical benefits of pet ownership and contact are well documented. The emotional bond between owners and pets can be as important to the owner as human relationships and provide similar psychological benefits. Numerous health benefits including reduction in distress, anxiety, loneliness, and depression are associated with animal interaction.\(^2\) Ownership of some animal species (e.g., dogs) increases exercise and thus directly improves physical health.

Children brought up with companion animals have better social skills, self-esteem, and empathy than children without pets.\(^3\) In adults and the elderly, studies have documented an association between pets and reduced risk of cardiovascular disease, higher survival rates from myocardial infarction, and improved psychological and physical well-being among the elderly.\(^4\) Health benefits are also well documented in individuals who are immunocompromised. Such individuals may spend considerable time alone, and thus are especially vulnerable to mental and physical illness. Among individuals infected with HIV, domestic animals are often perceived as family members, serve as sources of support and affection, and protect against loneliness.\(^5\)

**IMMUNOCOMPRIMISING CONDITIONS**

People may be immunocompromised for various reasons. It is important to remember that people are not simply immunocompromised or not; there is a degree to which people are immunocompromised, and this varies between and within conditions. Primary immunodeficiencies are those that result from genetic causes, while acquired immunodeficiencies result from nongenetic causes. Although both are important, acquired immunodeficiencies are much more common causes of immune dysfunction. Acquired immunodeficiencies include: 1) transplants (bone marrow and solid organ); 2) infectious diseases (e.g., human immunodeficiency virus [HIV] infection); 3) metabolic diseases (e.g., diabetes mellitus, renal disease); 4) splenectomy; 5) cancers; 6) drugs (e.g., high doses of steroids, chemotherapeutics); and 7) physiologic factors (e.g., malnutrition, extremes of age, and pregnancy). It is estimated that up to 20% of the United States population has some degree of immunosuppression, with similar statistics likely applying to most developed countries.\(^6\)
HEALTH RISKS OF ANIMAL OWNERSHIP

Despite the established benefits of pet ownership and interaction, companion animals are a potential source of numerous human diseases. As a general rule, immunocompromised people are more likely to get sick from something that would not hurt an immunocompetent person, and they are more likely to develop serious illness or complications from something that would only cause mild disease in others. For example:

- Individuals infected with HIV are at 20–100 times greater risk of *Salmonella* bacteremia than those without HIV infection.\(^8\)
- *Capnocytophaga canimorsus* is a member of the normal oral bacterial flora of dogs and cats. Alcoholics, asplenic individuals, and immunocompromised individuals are at risk for severe (often deadly) *C. canimorsus* infection following dog/cat licks or bites.
- Individuals with hematologic malignancies are twice as likely to be infected with *Campylobacter* than those without cancer, and illness is more likely to be severe and prolonged in these individuals.\(^9\)
- *Bordetella bronchiseptica* can cause severe illness in immunocompromised individuals.

See Table 1 for additional examples and information.

Table 1. Pet-associated infections particularly relevant to immunocompromised individuals

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Frequency or risk in immunocompromised individuals</th>
<th>Common clinical manifestations in general population (and immunocompromised)</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Moderate</td>
<td>Subclinical or self-limited febrile illness (greater risk for <em>in utero</em> infection, encephalitis)</td>
<td>Most cases among transplant recipients and those with HIV infection caused by reactivation (3–26 wks post-transplant); food and environment are main sources of human infection</td>
</tr>
<tr>
<td><em>Cryptosporidium</em> spp.</td>
<td>Moderate; 3–6% of HIV-infected individuals; risk increases with degree of immunosuppression and is largely limited to those with impaired T-cell function</td>
<td>Subclinical or self-limiting diarrhea (chronic intractable diarrhea, shortened survival; symptoms dependent on immune status and genotype/species of infection)(^16)</td>
<td>All species identified in companion animals should be considered potentially zoonotic(^16)</td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td>Low; incidence of bacteremia 20- to 100-fold higher among HIV-infected than among HIV-uninfected individuals(^8)</td>
<td>Self-limiting diarrhea, vomiting (higher rates of bacteremia, severe systemic and localized infections)</td>
<td>Chemotherapy-triggered reactivation of asymptomatic colonization occurs</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>Low; greater rate in</td>
<td>Self-limiting diarrhea,</td>
<td></td>
</tr>
</tbody>
</table>

jejuni patients with hematological malignancy vs. without malignancy (incidence rate ratio = 2.179) vomiting, fever (relapses of septicemia and diarrhea)

*Bartonella henselae* Low, but perhaps underdiagnosed Lymphadenopathy and fever (bacteremia, proliferative lesions on the skin, liver or spleen)

*Giardia duodenalis* Low Subclinical or mild diarrhea (chronic diarrhea, weight loss) Species-specific assemblages: A-I (humans and animals), A-II (humans), A-III and A-IV (animals), B (humans and animals), C and D (dogs), E (cloven-hoofed animals), F (cats), G (rats)17

*Bordetella bronchiseptica* Rare Generally none (respiratory disease in children with lung transplants, those treated with immunosuppressive drugs, and HIV-infected)

*Capnocytophaga canimorsus* Rare Generally none (sepsis, disseminated intravascular coagulation, death especially among asplenic persons, those of advanced age, or alcoholics)

**PET OWNERSHIP AND PRACTICES BY IMMUNOCOMPROMISED INDIVIDUALS**

Studies indicate that pet ownership practices by immunocompromised individuals are very similar to that of the general population, with 50–60% of surveyed groups with cancer, HIV infection and transplant recipients owning pets. Furthermore, the distribution of species owned mirrors that of the general population, with dogs and/or cats being the most common pets, but other species (e.g., birds, pocket pets, reptiles/amphibians) also reported. High-risk pets (those believed to pose the greatest health risk due to an elevated frequency of pathogen colonization and/or shedding), including dogs/cats < 6 months of age, exotic species, rodents, and reptiles/amphibians, are often owned by immunocompromised individuals.10 A study among households with children diagnosed with cancer, noted that over 70% of households that obtained a new pet following diagnosis, acquired a high-risk pet.10 Pet husbandry practices that increase zoonotic disease risk have been frequently documented among immunocompromised individuals. In one study, high-risk foods (i.e., raw eggs, raw meat, or raw animal product treats) were fed to dogs in 21% of households with children diagnosed with cancer.11
Furthermore, infection control practices among pet owners who are immunocompromised appear to be no more stringent than those practiced by lower-risk individuals.

**Zoonotic Disease Education**

Despite an increased risk for pet-associated disease, it appears a minority of high-risk pet owners receive education on ways to prevent zoonotic infections. Among households with children recently diagnosed with cancer, only 32% of respondents recalled having received zoonotic disease information from any source (including physicians and veterinarians). This proportion is similar to that recalled by the general population. The limited recall of zoonotic disease education by immunocompromised individuals is concerning and an area in which veterinarians and their staff can make significant contributions.

**Guidelines to Reduce Pet-Associated Health Risks**

The risk of disease transmission between pets and people is a function of pet and human-related factors. These factors include animal species, diet, age, opportunity for exposure (hospitalization, level of confinement), immunosuppression, and personal hygiene. By targeting these factors, we can dramatically reduce the disease risks facing immunocompromised individuals.

Being immunocompromised is not a contraindication to having a pet. However, individuals who are immunocompromised, and households with such individuals, should be more cautious than other pet owners of ensuring their pets remain healthy and following precautions to reduce transmission of pathogens from pets. Pet contact guidelines can be categorized into 1) personal hygiene, 2) types and ages of animals, and 3) pet health and husbandry practices (Table 2). These guidelines are general; several recently published resources should be consulted for targeted information for specific human and veterinary medical conditions. Clients that have specific questions about the risk to household members should be encouraged to consult with their physician.

**Table 2. Pet contact guidelines for households with immunocompromised individuals**

**Personal hygiene**
- Wash hands after handling animals or their environment; supervise handwashing for children < 5 yrs
- Avoid contact with pets’ feces and animal-derived pet treats
- Promptly wash bites and scratches from animals; do not allow pets to lick open wounds or broken skin
- Have someone who is not immunocompromised clean litter boxes/cages/aquariums (if that is not possible, wear gloves); do not dispose of aquarium water in sinks used for food preparation or bathtubs

**Types and ages of animals**
- Avoid contact with dogs and cats < 6 months of age or strays
- Avoid contact with animals with diarrhea
- Avoid contact with young farm animals (e.g., petting zoos)
- Avoid contact with reptiles, amphibians, rodents, and baby poultry (chicks and ducklings) and anything that has been in contact with these animals; preferably these animals should not be kept in the households of immunocompromised individuals
- Reptiles, amphibians, rodents, and baby poultry should not be permitted to roam freely through a home or living area and should be kept out of kitchens and food-preparation areas
- Exercise caution when playing with dogs and especially cats, to limit scratches; keep pets’ nails short
- When acquiring a new pet, seek mature animals from established vendors
- Avoid contact with exotic pets and nonhuman primates
- When visiting other households with pets, take the same precautions with those pets
Pet health and husbandry
- Spay/neuter any pets to help decrease roaming tendencies and behavioral issues
- Keep cats indoors; change litter boxes daily; keep cats away from kitchens or other areas where food preparation and eating occur
- Keep dogs confined when possible; walk on leash to prevent hunting and eating garbage or feces
- Feed only canned or dried commercial food or well-cooked, home-prepared food; any dairy products should be pasteurized
- Prohibit access to non-potable water, such as surface water or toilet bowls
- Routine preventative care, including steps to control and prevent ecto- and endoparasites (e.g., ticks, worms) as indicated by the area
- Clean bird cage linings daily; wear disposable gloves (+/- surgical mask) when handling; dampen cage litter with water (mist) to decrease generation of dust
- Clean small rodent cages frequently
- Regularly (e.g., weekly) launder pet bedding
- Seek veterinary care at first sign of illness in an animal

Knowledge of Client’s Immune Status: Promoting and Safeguarding Client Disclosure
Given the increased pet-associated disease risk for immunocompromised individuals, it is important for veterinary staff to be aware of these conditions and provide targeted education and recommendations to those clients. It appears, however, that most veterinarians are not aware of their clients’ immune status (only 66% in one study\textsuperscript{15}), making such targeted efforts difficult. Techniques that utilize passive (e.g., pamphlets, signs) and active (intake questionnaire) formats can be effective in encouraging clients to disclose the immune status of individuals in their household. Brochures and posters are available from a number of sources (e.g., the Centers for Disease Control and Prevention Healthy Pets - Healthy People, Pets are Wonderful Support, Worms and Germs Blog - Ontario Veterinary College). Some advocate utilizing intake questionnaires to obtain information for the client’s household, such as asking if there are any children less than 5 years of age, people with immune problems, or women who may be or are planning to become pregnant.\textsuperscript{13}

Veterinary clinic staff must recognize, however, that such client’s personal health information may be considered confidential and protected under privacy laws. The greatest concerns focus on how this information is secured and provided to other individuals (e.g., clinic staff, other veterinary clinics). As such, veterinary clinics need to decide how such information is recorded, if at all. If information is recorded, it is best to ensure clients are aware (and provide written consent) as to why the information is requested, how the information will be used, and, if included in the patient’s record, may be transmitted to other veterinary clinics as part of the patient’s record. This consent should be reviewed with the client on a regular basis.

References
Common Cases and Questions in Veterinary Infection Control

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**INTRODUCTION**

It is estimated that 30–70% of hospital-associated infections (HAIs) that occur in human hospitals are preventable through common infection control practices. Although data are not available for veterinary medicine, it is reasonable to assume similar statistics apply. Furthermore, veterinary staff are at an increased risk for certain animal-derived infections. Efforts directed toward risk reduction (e.g., hand hygiene, personal protective equipment (PPE), cleaning and disinfection), risk assessment (e.g., surveillance), and education can reduce HAIs for veterinary patients, staff, and clients. Establishing and maintaining an infection control program is paramount to integrating these efforts. Here, we discuss some of the most common (and important) scenarios and topics about which veterinary infection control personnel are consulted.

1. **COMMON PATHOGENS THAT ARE OFTEN MISUNDERSTOOD OR HAVE IMPORTANT PUBLIC HEALTH IMPLICATIONS**

*Salmonella* and *Leptospira* are often encountered in veterinary practice and as zoonotic pathogens can have important implications for veterinary staff and clients.

**a. Salmonella**

Overall, the prevalence of *Salmonella* in feces of owned dogs and cats is approximately 0–4%, with similar findings in healthy and diarrheic pets. The prevalence is markedly increased if pets are fed raw meat/egg products (~ 30–70%). In general, antimicrobial administration is not warranted for uncomplicated *Salmonella* infections; the presence of systemic disease or an immunocompromised patient may alter this decision.\(^1\) Due to the zoonotic potential of this pathogen, client education is warranted if *Salmonella* is detected or if high-risk husbandry factors such as feeding raw meat/egg products are present. Precautions at home should include added diligence to hand hygiene after handling the animal and particularly after handling feces/soiled litter, limiting the area where dogs are allowed to defecate outside, restricted access to certain areas such as the kitchen and possibly individuals’ bedrooms, and safe handling of raw food/treats, food dishes and utensils. People at greatest risk for infection and complications are those less than 5 years of age, over 65 years of age, pregnant, or immunocompromised. Nosocomial transmission of *Salmonella* patient-to-patient and patient-to-staff have been documented in small animal clinics. In the clinic, dogs and cats with idiopathic diarrhea or diagnosis of infection with *Salmonella* should be handled as if contagious (housed in isolation, use of PPE including gloves and gown/secure lab coat, restricted access to other areas of the clinic/outdoors, enhanced cleaning and disinfection procedures, strict hand hygiene).

**b. Leptospira**

Dogs with leptospirosis can serve as a source of this pathogen for clinic staff. Although such events do not appear to be common, simple steps can be taken to further reduce this risk. In order to be effective, infection control practices should be implemented as soon as leptospirosis is considered a reasonable differential. Since test results are often negative during the acute phase of disease or test results may be delayed, it is prudent to consider all dogs with acute renal or hepatic disease, or where there is a reasonable possibility of leptospirosis, as leptospirosis suspects until an alternative diagnosis has been made. Treatment with an appropriate antibiotic (i.e., intravenous ampicillin or, if tolerated, oral doxycycline) should be started or continued if the animal is being treated at the time of admission. Precautions should be taken, including PPE (gloves, gowns, booties if potential contamination of floor, face protection if urine splashing is a risk) and reduced movement of the animal, until appropriate
antibiotic therapy has been given for at least 48 hours. Thereafter, the risk of shedding viable *Leptospira* in the urine is greatly reduced. As a contaminated hair coat can be a risk for transmission, consider bathing leptospirosis suspects with a chlorhexidine-containing shampoo followed by hot air drying after 48 hours of appropriate antimicrobials have been administered.²

2. **COMMON PATHOGENS THAT RECEIVE LITTLE ATTENTION, BUT CAN HAVE IMPORTANT ZOONOTIC DISEASE IMPLICATIONS**

Cats and dogs harbour various commensal organisms that can have important public health consequences. In general, these organisms do not cause disease in animals, so veterinarians are often unaware of their potential human health consequences. *Capnocytophaga canimorsus* (the agent of dog bite septicemia) and *Pasteurella multocida* are two such organisms. Both are present in the vast majority of dogs’ and cats’ mouths. Bites, scratches or other close contact can result in transmission of the organisms. These pathogens can result in severe (even fatal) infections in people, particularly in certain high-risk groups (notably immunocompromised, asplenic, alcoholics and extremes of age). Such individuals should be made aware of the risk of severe human disease and measures to reduce disease risk, such as preventing/minimizing bites and scratches, need for medical evaluation (and antimicrobial prophylaxis) following dog or cat bites, and minimizing saliva contact with mucous membranes (not permitting licking of the face), ulcers, wounds, and invasive devices and associated materials such as dialysis tubing. Good hygiene measures during and after pet contact are critical for those at high risk for disease. Veterinary staff should consider mechanisms to inquire if high-risk people live in or visit their clients’ households so that appropriate recommendations can be provided (see notes for the talk *Worms & Germs - Zoonoses and Immunocompromised Clients* for more information).

3. **DEALING WITH AND AVOIDING ENVIRONMENTAL CONTAMINATION**

The level of concern and infection control attention given to a particular disease or situation depends on a number of factors including what pathogen is suspected, how the pathogen is spread (i.e., direct contact, indirect contact [if survives in environment], droplet), and the level of disease risk to animals and staff. A number of resources are available to assist in determining the appropriate response.³,⁴ As most diagnostic tests are not available for days or weeks after submission, use of one or more risk reduction techniques (e.g., gloves/gowns, isolation, enhanced disinfection) should be used for animals in which an infectious disease is confirmed, as well as those for which there is a reasonable suspicion (e.g., animal with suspected infectious diarrhea).

When contamination has already likely occurred (such as a parvovirus-positive dog that was present in the general waiting area), it is important to act quickly, with appropriate control and prevention responses. Such a response would include: reducing further contamination (moving the dog into an isolation ward or overflow examination room, with staff wearing appropriate PPE); closing off the contaminated area to further use until cleaned and disinfected; cleaning and disinfecting all contaminated areas. It is critical that floors and common surfaces are first cleaned of all visible contamination, then dried and an appropriate disinfectant applied at the recommended dilution and contact time. Resources are available to determine the appropriate disinfectant for a suspected pathogen.³ These materials should be readily available for staff and ideally part of a Standard Operating Procedure (SOP) for such occurrences to ensure response is quick and appropriate. A commonly used protocol is to clean and disinfect a room and then allow it to stand empty for several hours or overnight. This can sometimes be inconvenient in critical areas and in reality is not particularly effective. Pathogens that would die in the environment over this period of time would generally be killed by any properly applied disinfectant, and those not killed by the disinfectant are unlikely to die over the same period. It is far more effective to simply let the room dry, then perform an additional round of disinfection to help ensure all surfaces have been thoroughly treated, and reopen the room when it has dried once again.
Owners of other pets likely exposed to the pathogen in the process should be counselled on early signs of disease and appropriate steps in reducing further transmission. This is best done in a proactive, upfront manner even if clients may initially be upset, as it is the best way to ensure that any animals that do get sick are diagnosed and treated as quickly and appropriately as possible.

Although rapid response to an infection control situation is important, it is far easier to prevent such situations before they occur. Routine screening by front office staff at the time of admission (e.g., asking if the animal has had episodes of vomiting or diarrhea within the past 48 hours) can ensure precautions are taken with animals with a suspected infectious disease. Precautions will vary with the level of concern and pathogen suspected, but may include having the animal and client wait outside the clinic before the appointment, admitting the animal through a separate entrance directly into an examination area, ensuring all staff having contact with the animal wear the appropriate level of PPE, or admitting the animal directly into isolation.

4. MANAGING ZOONOTIC DISEASE RISKS AMONG STAFF AND CLIENTS

In order for an infection control program to be successful, staff and clients must be educated about the program and what risks are present for animals and themselves. An understanding of why particular precautions are taken is critical to achieving compliance and ensuring that individuals are not tempted to “cut corners.” Communication is key. All educational materials and trainings provided to staff and clients should be documented (given the increasing potential for lawsuits surrounding such situations, documentation is especially important). A number of resources are available that provide reliable, balanced, client or veterinary staff-appropriate fact sheets for many of the common infectious diseases encountered in veterinary medicine.4,5 Ensuring staff and clients are provided timely education will improve infection control compliance, promote a safer work environment, and help clients and their pets live happier and healthier lives.

5. DON’T DISCOUNT/TAKE LIGHTLY VACCINE-PREVENTABLE DISEASE

In the case of certain diseases for which animals are typically vaccinated, there appears to be an ambivalence or limited concern in the veterinary community when it comes to infection control. The clinic setting can be an important propagator of gastrointestinal and upper respiratory pathogen transmission. Factors such as inadequate or waning immunity to vaccine-preventable disease (extremes of age, comorbidities, other reasons for immune suppression), high-risk populations, incomplete protection from vaccine (true for most vaccines), close proximity, and frequent direct or indirect contact between patients all increase the risk for vaccine-preventable pathogen transmission. As such, infection control measures are equally important with some of the more “mundane,” yet highly transmissible, pathogens (e.g., Bordetella, herpesvirus, calicivirus, parainfluenza virus). Hospital-acquired infection with such agents can lead to morbidity, mortality (most often in high-risk patients) and poor public relations with staff and clients. Early recognition and implementation of infection control measures can make all the difference in stopping second-generation transmission. To be successful, staff must know to look for and immediately report key syndromes (e.g., coughing, sneezing, diarrhea), ideally as part of an infection control plan.

6. TO TEST OR NOT TO TEST?

This is a very common question that comes up in any number of scenarios for a wide variety of pathogens and animals. Ultimately it boils down to what is going to be done with the results. What will be done if the test is positive? What will be done if the test is negative? If the answer is the same for both, then generally the answer to the initial question is: don’t do the test. This is particularly true for otherwise healthy animals that are “screened” for pathogens (often using broad PCR-based panels lacking sufficient specificity to be of any real use). For example, a healthy animal living in an average
household tests negative for methicillin-resistant *Staphylococcus aureus* (MRSA). This does not preclude that the animal may have been exposed to MRSA since the test, or may subsequently be exposed, so in order to reduce the risk of transmission to or from the animal, recommendations would include avoiding high-risk contact (e.g., nose or perianal contact) and practicing good hand hygiene. If the animal tests positive for MRSA, there is no indication to treat the animal, as most will clear colonization over time if reexposure is avoided. Therefore, to reduce the risk of transmission to or from the animal, recommendations would include avoiding high-risk contact and practicing good hand hygiene. It is important to bear in mind that the clinical management of the animal is not the only consideration. For example, obtaining a definitive diagnosis and antimicrobial susceptibility panel in a case of clinical infection, even if it is already responding to treatment, provides useful information for assessing the risk/likelihood of the same infection occurring in other household or local animals, and it can help inform initial empirical therapy in subsequent cases, thereby making testing worthwhile.

7. Dealing with Multidrug-Resistant (MDR) Pathogens

It is important to remember that MDR bacteria cause infections identical to those of their antimicrobial-susceptible counterparts - clinically there is no way to tell them apart. The only way to identify an MDR pathogen is through properly standardized antimicrobial susceptibility testing, which also provides the best information for determining treatment. With the increasing prevalence of many of these resistant bacteria, routine and timely culture of all suspected infections is crucial to help avoid treatment failures, and their various consequences, without the abuse of “big gun” antimicrobials that should only be used as a last resort. These two factors - culture and susceptibility testing and prudent antimicrobial use - are key to slowing the emergence and spread of MDR pathogens. Other important measures in the “battle against the superbugs” include improving awareness and implementation of basic infection control measures in veterinary clinics (and at home), increasing use of non-antimicrobial/adjunct modalities for treating infections where applicable, and instituting and integrating local and regional surveillance programs.

A note on methicillin-resistant (MR) staphylococci in particular: There is concern that MR *S. pseudintermedius* (MRSP) can be mistaken for MRSA (or vice versa) in the laboratory if proper speciation is not performed. It is important that veterinary samples are submitted to a laboratory that is able to accurately make this distinction between isolates. The most significant difference between the two is not that they are treated differently, but that MRSP has a much lower potential for zoonotic transmission. Anecdotally, some MRSP isolates appear to be resistant to a broader range of antimicrobials than even MRSA isolates, making appropriate susceptibility testing even more crucial to help guide therapy.

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Pets & Public Health - Are We Getting the Message Across?
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INTRODUCTION
Veterinarians play an important role in promoting public health through education of clients regarding zoonotic disease risks. Conveying the balance of the risks and benefits of animal contact can be difficult given time and privacy constraints with clients, as well as stigma or misinformation regarding some animal-related topics or human disease conditions. Understanding important knowledge gaps, attitudes, and high disease-risk practices of the public allows for targeted, effective discussions with clients on this topic.

PET OWNERSHIP AND THE GENERAL PUBLIC
In a recent survey of the general population of Ontario, Canada, 64% of participants currently had a pet in their household.¹ Pet ownership remained high (55%) for households with individuals at higher risk for zoonotic infections (i.e., < 5 years, ≥ 65 years, immunocompromised),¹ including households with children diagnosed with cancer (63%).² Species owned appear to be similar between higher- and lower-risk households and included dogs (68%), cats (48%), fish (13%), exotic mammals (7%), such as hamsters, and reptiles and birds (each 6%). Most (77%) households with a child previously diagnosed with cancer that obtained a new pet, acquired a high-risk pet. Although general pet ownership is typically not discouraged for those at high risk for infectious disease, in most situations high-risk pets should not be acquired or, if present, should be temporarily housed elsewhere until the risk of infectious disease is lower. The placement of high-risk pets into high-risk households should be discouraged and is an important educational topic for clients. For the delivery of this message to be most effective, veterinary staff must be aware of the current general disease risk of their clients’ households (e.g., are there members or frequent visitors who are very young, elderly, immunocompromised, or pregnant); see Advising Clients from High-Risk Households. However, it is still important to remember that lower-risk households are not no-risk, and the status of a household can change either rapidly or gradually. All pet owners can therefore benefit from education about zoonotic disease risks and simple, everyday ways to mitigate them.

What Does the Public Know About the Potential Risk of Pet-Associated Zoonotic Disease?
Recent research suggests not very much. When given a list of 11 infectious pathogens, respondents from the general population were only able to correctly classify just over half based on their potential to be transmitted from pets to people. These results were similar regardless of if there were high-risk household members (and thus one would hope knowledge level would be higher than the general public).¹² Perhaps this is not overly surprising, as a minority of individuals (36%) recalled having ever received information regarding pet-associated disease risks. Perhaps most concerning is that most respondents were comfortable with their current level of knowledge, and thus perhaps unlikely to seek additional information or implement suggested changes.

Despite a number of readily available brochures and posters on pet-associated zoonotic disease offered from reliable sources (e.g., the Centers for Disease Control and Prevention Healthy Pets - Healthy People, Pets are Wonderful Support, Worms and Germs Blog - Ontario Veterinary College), it appears many veterinary clinics do not utilize such resources (in one study,³ only 57% of veterinary practices had such materials available to clients). The availability of these resources to clients (in waiting rooms, on websites, provided when indicated by a topic of discussion) may be helpful in educating clients and promoting active discussion. Additionally, techniques that utilize active formats (e.g.,
veterinary staff initiating discussion) may be helpful, due to individuals’ aforementioned comfort with an often deficient knowledge level.

**What Pet Husbandry Practices Occur in Households That May Increase Disease Risk?**
The way in which we interact with our pets can play an important role in disease risk. In one survey, dogs were reported to lick a household child’s face at least several times per week in ~ 24% of households. As pets harbour many commensal organisms in their oral cavity that can result in significant disease in high-risk people (e.g., *Capnocytophaga canimorsus*), and can cause infection even in healthy individuals (e.g., *Pasteurella multocida*), and particularly in the case of coprophagic animals that could potentially harbour enteropathogens in their mouths, this practice should be discouraged. Household children were often involved in cleaning up pet fecal material (25–63%). Additionally, practices that increase zoonotic disease risk were frequently identified in many households; some fed high-risk foods (i.e., raw eggs, raw meat, or raw animal product treats) to their dogs (28%) or cats (3%); 14% of reptile-owning households allowed the pet to roam through the kitchen or washed it in the kitchen sink. These practices are important routes for pathogen transmission that could be easily avoided if clients are made aware that lower-risk alternatives exist. Another often controversial practice is allowing pets to sleep on a person’s bed. Many people (and many animals!) find sleeping with their pet (owner) very comforting, so there are benefits. From an infection control standpoint, in addition to factors such as the type of pet and the immune status and age of the owner, a key consideration is what constitutes “on the bed.” The lowest risk situation is likely a pet that sleeps at the foot of the bed, ideally on an additional blanket that can be washed regularly. The opposite of this is the pet that sits and sleeps on a person’s pillow (either when the person is there or not), as there is obviously a high degree of face/mouth/mucous membrane contact with the pillow, and anything the animal may have shed on it. The key is not necessarily to tell all clients what practices should and should not be done, but to make them aware of the risks and the alternatives, so they can make the decision themselves.

**Advising Clients from High-Risk Households**
Knowledge, attitudes and practices surrounding pet-associated zoonotic diseases appear to be similar for households with and without high-risk members. It is particularly important not only for individuals in high-risk households to be given information about mitigating infectious disease risks, but also to help them understand the information and how to implement safer practices. The key appears to be to identify high-risk households so that effective, targeted discussion can occur. In one study, pet owning respondents with children previously diagnosed with cancer that visited a veterinarian recalled that veterinarians rarely (14%) inquired about the immune status for household members. All who were asked about their child’s medical condition told the veterinary staff about their child’s condition, while only approximately half of those not asked provided the staff with this information. Thus, if staff ask, chances are clients will supply information about household-disease risk. (Note: See the talk *Worms & Germs - Zoonoses and Immunocompromised Clients* for important information on promoting and safeguarding client disclosure). However, when veterinary staff were informed of the child’s condition, in few cases (30%) did the veterinarian make any specific comments about the pet in relation to the child’s medical condition. If veterinary staff ask about household-disease risk, it is important to be prepared to provide targeted education and/or direct clients toward resources to address questions. (Note: See the talk *Worms & Germs - Zoonoses and Immunocompromised Clients* for specific ownership and husbandry recommendations that should be considered with high-risk households; there are also a number of additional resources on this topic).

**Therapy Pets**
Most companion animals have a limited ability to spread infection in terms of the number and types of people with which they have contact. However, “therapy pets,” such as those used in hospital/patient
visitation programs and other types of animal-assisted interventions or activities (AAAs), have contact with a much larger number of people than the average household pet. Furthermore, these people, being patients in hospitals or residents of long-term care centers or similar facilities, are at higher risk for infections and complications thereof. It is therefore understandable why the health status, carrier status (in terms of zoonotic pathogens), and the type of human-animal interactions of therapy pets should be carefully scrutinized.

A cross-sectional study of 102 therapy dogs in Ontario, Canada reported that at least one zoonotic agent was isolated from 80% of the animals involved. Toxigenic strains of *Clostridium difficile* were the most common, being isolated from the feces of 41 (40%) dogs, and another 17 (17%) dogs were shedding non-toxigenic strains of *C. difficile*. Other potentially zoonotic agents identified in small numbers of animals from this group included multidrug-resistant *Escherichia coli*, *Salmonella*, *Giardia*, roundworms and hookworms.\(^{10}\) It has been shown that dogs involved in AAAs in healthcare facilities are at greater risk of acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) and *C. difficile* than dogs involved in non-healthcare-related AAAs. Licking patients and accepting treats were significant risk factors for acquiring these pathogens.\(^{11}\) Furthermore, it has been shown that dogs’ hair coats can be transiently contaminated with MRSA, *C. difficile* and potentially other pathogens (both zoonotic and non-zoonotic) that they may encounter in a healthcare or long-term care facility.\(^{12}\) Lefebvre & Weese\(^ {12}\) showed that MRSA contamination of a therapy pet’s hair coat could be transferred to a person’s hand after one minute of petting. Another study implicated a resident cat in transmission of MRSA between patients at a long-term care facility. Reasonable precautions should be taken to reduce the potential risk of pathogen transmission between patients and therapy pets.\(^ {13,14}\)

Every time a person has contact with an animal, there is a risk of transmission of any number of infectious pathogens. (The same is also true every time a person has contact with another person.) Factors that can increase the risk of infection include decreased immunity in the person, increased virulence of pathogen, and increased contact with the animal (making it more likely for transmission to occur, or resulting in transmission of a larger number of infectious organisms). In a hospital or long-term care facility setting, it is not possible to control the health status of individuals, as their compromised state is often the very reason they are there. However, it is prudent to restrict or at least modify the kind of animal contact that occurs with the most severely ill and susceptible patients.

The virulence and number of organisms being shed by therapy pets cannot be directly controlled (or even predicted) in many cases, but there are a few measures that can be taken to help reduce this risk. Animals showing overt signs of illness (including systemic, gastrointestinal, respiratory or dermatologic disease) should not enter health or long-term care facilities. A sick animal is more likely to be shedding pathogenic organisms and may be more prone to infection by organisms it encounters in the environment or through patient contact. In healthy animals, regular preventative healthcare and routine deworming and flea control are certainly important, but will only help to reduce or eliminate a small number of the organisms of concern. Potential risk factors that have been identified for carriage of various zoonotic pathogens in cats and dogs include age and source: young animals (less than one year of age) and animals kept in high-density populations (e.g., shelters, kennels/catteries) may be more likely to shed parasites such as *Giardia*, *Cryptosporidium*, *Toxoplasma*, roundworms and hookworms. Likewise, cats that are allowed to roam outdoors and hunt are more likely to shed some of these organisms, as well as *Salmonella*. It can also be difficult to predict the temperaments of very young animals (less than one year of age), and bites and scratches may occur more commonly from aggression, fear, or play. Therefore, in order to reduce the risk to patients, it is reasonable (and logical) to exclude these types of animals from being therapy pets. Therapy pets also need to be clean and well groomed, as this reduces contamination of the hair coat (minute amounts of fecal matter are of particular concern), as well as shedding.
As with pet ownership, many individuals may stand to benefit from AAAs, but the benefits must be weighed against the potential risks for each patient and each animal. Giving careful consideration to which patients can be visited, what animals should be allowed to visit, and reasonable precautions for reducing potential pathogen transmission during patient-animal interactions can help to reduce (though never eliminate) the infectious disease risks inherent to AAAs.

**PETTING ZOOS**

Petting zoos and other animal exhibits facilitate contact of the public with live animals as part of agricultural fairs and other seasonal or permanent attractions. They are entertaining but also serve an important educational function for individuals of all ages regarding animals and animal husbandry, and they also help to increase compassion for animals of different kinds. However, as with any type of human-animal contact, there is an associated risk of infectious disease transmission, which varies according to the animals involved, the individuals in contact with them, and the degree of contact that occurs. Risks are higher for young children, with whom petting zoos and similar events are often particularly popular, but elderly and immunocompromised individuals may also visit such exhibits. This is yet another area in which veterinarians, even if they normally deal exclusively with companion animals, are uniquely suited to offer information and advice to members of the public for the benefit of public health.

Numerous disease outbreaks have been associated with animal contact at public venues. The most commonly reported pathogen in these outbreaks is *Escherichia coli* O157:H7, but other pathogens include *Salmonella*, *Cryptosporidium*, *Giardia*, *Coxiella burnetii* (Q fever) and dermatophytes (ringworm). There is also potential risk for the transmission of other zoonotic pathogens including *Campylobacter* and rabies. Several organizations have published recommendations for management of live animal exhibits such as petting zoos, intended to help decrease the risk of infectious disease transmission from animals to the public, but implementation of these recommendations is still poor in many facilities.

According to the National Association of State Public Health Veterinarians, “the recommendation to wash hands is the most important prevention step for reducing the risk for disease transmission associated with animals in public settings.” However, hand hygiene compliance at petting zoos and similar public exhibits has been reported to be poor, and failure to perform hand hygiene has been identified as a significant risk factor for disease in numerous outbreaks associated with such events. This is less likely to be due to increased awareness of the need for hand hygiene among children, rather than due to parents instructing children to perform hand hygiene after visiting the exhibit but failing to do so themselves. While healthy adults are at lower risk of infection than children, it is still equally important for parents and guardians to perform hand hygiene, as indirect transmission may result from contamination of their own hands followed by close contact with their children.

The risk of infectious disease transmission between animals and people in any setting can never be completely eliminated. However, by increasing adherence to management and safety recommendations and increasing hand hygiene compliance among visitors at public animal exhibits, the risk can be reduced. This will allow these exhibits to continue to play their role in educating the public about animals and animal husbandry and promoting compassion towards different animal species.

**ENDNOTE**

Some species are considered to be “high risk,” as data on pathogen carriage and/or zoonotic transmission has resulted in established guidelines recommending their exclusion or cautioning ownership in households with high disease-risk individuals. This list includes dogs/cats < 6 months of age, reptiles, amphibians, rodents, baby poultry and exotic species.
REFERENCES


Rhodococcus equi Infections in Foals
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INTRODUCTION
Rhodococcus equi, a gram-positive facultative intracellular pathogen replicating in macrophages, is one of the most important causes of disease in foals between 3 weeks and 6 months of age, with most foals showing clinical signs before the age of 4 months. R. equi has also been increasingly recognized as an important cause of pneumonia in immunosuppressed people, especially those infected with HIV. R. equi is considered to be a saprophytic inhabitant of the soil. Although all horse farms are likely to be infected to various degrees with R. equi and antibody is widespread in the horse population, the clinical disease is enzootic and devastating on some farms, is sporadic on others, and is unrecognized on most. This probably reflects differences in environmental (temperature, dust, soil pH, soil type) and management conditions as well as differences in virulence of isolates. On enzootic farms the disease leads to significant financial loss because of the cost of therapy and occasional death of foals.

Although the virulence of R. equi likely depends on many determinants, isolates from pneumonic foals characteristically contain a large plasmid which encodes a gene responsible for the expression of a virulence associated protein (VapA) on the surface of the bacteria at temperatures > 34°C. Foals experimentally infected with virulent (plasmid containing) R. equi develop severe pneumonia whereas plasmid cured derivatives are rapidly cleared and fail to induce lesions. Inhalation of dust particles laden with virulent R. equi is the most important route of pneumonic infection in foals. Ingestion of the organism is a significant route of exposure but does not lead to hematogenously acquired pneumonia unless the foal has multiple exposures to very large numbers of bacteria.

CLINICAL MANIFESTATIONS
The most common manifestation of R. equi infections in foals is a chronic supplicative bronchopneumonia with extensive abscessation. The slow spread of the lung infection combined with the remarkable ability of foals to compensate for the progressive loss of functional lung, make early clinical diagnosis difficult. Early clinical signs often only consist of a mild fever or a slight increase in respiratory rate that may not be apparent unless foals are exercised or stressed by handling. As the disease progresses, clinical signs may include decreased appetite, lethargy, cough, fever, tachypnea, and labored breathing. Nasal discharge is an inconsistent finding.

Because ultrasonographic screening for early detection has become routine practice at many farms endemic for pneumonia caused by R. equi, the most frequently recognized form of R. equi infection on those farms is a subclinical form in which foals develop ultrasonographic evidence of peripheral pulmonary consolidation or abscessation without manifesting clinical signs. On those farms, the cumulative frequency of sonographically visible areas of focal pulmonary consolidation or abscessation considerably exceeds the historical frequency of clinical pneumonia attributed to R. equi indicating that many subclinically affected foals might spontaneously recover without therapy. In 2 independent studies at endemic farms, 80% to 90% of foals with ultrasonographic lesion recovered without antimicrobial therapy. The proportion of such subclinically affected foals that progress to clinically apparent disease might vary by farm, geographical region, and age at which foals are examined.

Extrapulmonary manifestations of rhodococcal infections are common. In a retrospective study of 150 foals with R. equi infections, 111 (74%) had at least 1 of 39 extrapulmonary disorders. Survival was significantly higher among foals without extrapulmonary disorders (32/39 [82%]) than among foals with extrapulmonary disorders (48/111 [43%]), but many such disorders were only recognized after death. Intestinal lesions are present in approximately 50% of foals with R. equi pneumonia presented for necropsy. However, the majority of foals with R. equi pneumonia do not show clinical signs of intestinal
disease. Abdominal lesions may include ulcerative enterocolitis and typhilitis over the area of the Peyer’s patches, granulomatous or suppurative inflammation of the mesenteric and/or colonic lymph nodes, or in some cases a single large abdominal abscess may be the only lesion.\(^7\) Polysynovitis is present in approximately 25–30% of cases with \(R.\ equi\) infections. The degree of joint effusion is variable and, in most cases, lameness is mild or absent. Cytological examination of the synovial fluid usually reveals a non-septic mononuclear pleocytosis and bacteriologic culture of the synovial fluid is negative.\(^8\) Immune-mediated processes may also contribute to the development of uveitis, anemia, and thrombocytopenia in some foals infected with \(R.\ equi\).

Bacteremic spread of the organism from the lungs or gastrointestinal tract may occasionally result in septic arthritis and, more commonly, osteomyelitis. However, foals can occasionally develop \(R.\ equi\) septic arthritis or osteomyelitis without apparent lung involvement or other source of infection. \(R.\ equi\) vertebral osteomyelitis or diskospondylitis resulting in spinal cord compression has also been reported. Other rare extrapulmonary manifestations of \(R.\ equi\) infections in foals include panophthalmitis, guttural pouch empyema, sinusitis, pericarditis, nephritis, and hepatic, renal, and intracranial abscessation.\(^6\)

**DIAGNOSIS**

The distinction between lower respiratory tract infections caused by \(R.\ equi\) and those caused by other pathogens is problematic especially in farms without previous history of \(R.\ equi\) infections. Diagnostic tests, including white blood cell concentration (WBC), measurement of fibrinogen concentrations, ultrasonography, and radiography, may help raise the degree of suspicion that pneumonia in a given foal may be caused by \(R.\ equi\) rather than by another microorganism. However, the definitive diagnosis of bronchopneumonia caused by \(R.\ equi\) should be based on bacteriologic culture or amplification of the vapA gene by polymerase chain reaction (PCR) from a tracheobronchial aspirate (TBA) obtained from a foal with 1) clinical signs of lower respiratory tract disease; 2) cytological evidence of septic airway inflammation; and/or 3) radiographic or ultrasonographic evidence of bronchopneumonia. Amplification of vapA by PCR may be done in conjunction with, but should not replace, bacterial culture because it does not permit identification of other bacterial pathogens and *in vitro* antimicrobial susceptibility testing of \(R.\ equi\) isolates.\(^9\) The definitive diagnosis of extrapulmonary infections (e.g., abdominal abscess, osteomyelitis) caused by \(R.\ equi\) must rely on bacteriologic culture or PCR amplification of vapA from samples from the site of infection. The diagnosis of extrapulmonary disorders from sites at which \(R.\ equi\) cannot be detected (e.g., uveitis or polysynovitis) should be based on isolation of \(R.\ equi\) from a TBA or other primary sites of infection. The diagnosis of enterocolitis caused by \(R.\ equi\) is problematic because isolation of \(R.\ equi\) from feces cannot be taken as evidence of enterocolitis caused by \(R.\ equi\).\(^9\)

Hyperfibrinogenemia is the most consistent laboratory finding in foals with \(R.\ equi\) pneumonia, although rare cases may have normal fibrinogen concentrations. Neutrophilic leukocytosis with or without monocytosis is also common. One study showed significantly higher fibrinogen concentrations and white blood cell counts (WBC) in non-survivors than in survivors, whereas other studies showed no difference between the 2 groups. In one study, WBC >20,000 cells/\(\mu\)L, fibrinogen concentration > 700 mg/dL, and evidence of pulmonary abscessation were more likely to be found in foals with pneumonia caused by \(R.\ equi\) than in foals with pneumonia caused by other bacteria.\(^10\) However, there is a considerable overlap in distributions, which precludes the use of fibrinogen concentrations and WBC for diagnosis or prognosis for an individual foal.

Thoracic radiography is useful in evaluating the severity of pneumonia and in assessing response to therapy. A prominent alveolar pattern characterized by ill-defined regional consolidation is the most common radiographic abnormality. The consolidated lesions are often seen as more discrete nodular and cavitary lesions consistent with pulmonary abscessation. Although non-survivors tend to have more severe radiographic lesions than survivors, many survivors have very severe radiographic lesions thus radiographs should not be used as the sole criterion for prognostication and euthanasia.\(^11\)
Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas, but may not be as useful as radiography to evaluate the full extent of lung lesions since abscesses with overlying aerated lung will not be detected. However, in most horses and foals with pulmonary abscessation the periphery of the lung is affected, enabling the ultrasonographer to successfully image some of the abscesses. Early ultrasonographic lesions are nonspecific and may only include irregularities of the pleural surface. These lesions may progress to form focal areas of consolidation of various sizes. In more chronic cases, well-circumscribed, encapsulated abscesses can be detected. Ultrasonography is very useful in evaluating the severity of pneumonia and in assessing response to therapy, especially for equine practitioners who do not have access to thoracic radiography. Ultrasonography is also a useful tool for detection of some abdominal abscesses and for screening for R. equi-infected foals on farms where the disease is endemic (see section on control). Ultrasonographic or radiographic detection of lung abscesses raises the degree of suspicion that pneumonia in a given foal is caused by R. equi. However, detection of pulmonary abscesses, while commonly used as a screening test (see below), is not a definitive diagnostic test.

Independent studies evaluating the performance of serological tests available for diagnosis of infection caused by R. equi at endemic farms have demonstrated these tests have either low sensitivity, low specificity, or both. Improving either sensitivity or specificity of ELISA assays by changing the cut-off value of the tests could only be done to the detriment of the other. The presence of antibodies indicates exposure, subclinical infection, or maternal transfer of antibodies but it does not necessarily indicate infection leading to clinical disease. The current state of knowledge precludes serology being used as a diagnostic test for R. equi pneumonia.

TREATMENT
A wide variety of antimicrobial agents are active against R. equi in vitro. However, because R. equi is a facultative intracellular pathogen surviving and replicating in macrophages, and therefore causes granulomatus lesions with thick caseous material, many of these drugs are ineffective in vivo. For example, in one study all 17 foals with R. equi pneumonia treated with the combination of penicillin and gentamicin died despite the fact that all isolates were sensitive to gentamicin. The combination of rifampin and erythromycin became the treatment of choice in the 1980s and has dramatically reduced foal mortality since its introduction. In recent years, clarithromycin or azithromycin, 2 newer generation macrolides, often replace erythromycin in the combination with rifampin. Macrolides and rifampin are highly active against R. equi in vitro, but only exert bacteriostatic activity. Of the 3 macrolides listed above, clarithromycin is the most active against R. equi in vitro. The combination of a macrolide and rifampin is synergistic both in vitro and in vivo and the use of the two classes of drugs in combination reduces the likelihood of R. equi resistance to either drug. Rifampin and macrolides are lipid soluble, allowing them to penetrate cell membranes and caseous material.

Advantages of azithromycin and clarithromycin over erythromycin in foals include enhanced oral bioavailability, prolonged half-lives, and much higher concentrations in bronchoalveolar cells and pulmonary epithelial lining fluid. These properties of the newer generation macrolides contribute to their lower dosages and longer dosing intervals. Concentrations of clarithromycin in pulmonary epithelial lining fluid and bronchoalveolar cells of foals at steady state are considerably higher than concentrations reported following daily administration of azithromycin to foals. However, clarithromycin concentrations at these sites decrease rapidly, whereas the release of azithromycin from cells is much slower, resulting in sustained concentrations of azithromycin in tissues for days following discontinuation of therapy. In a retrospective study, the combination clarithromycin-rifampin was significantly more effective than erythromycin-rifampin or azithromycin-rifampin, especially in foals with severe radiographic lesions.
Although well tolerated by most foals, macrolides commonly cause diarrhea. Most of the time the diarrhea is self-limiting and does not necessitate cessation of therapy but affected foals should be monitored carefully because some may develop severe diarrhea, leading to dehydration and electrolyte loss that necessitate intensive fluid therapy and cessation of oral macrolides. The incidence of diarrhea in foals treated with erythromycin-rifampin has ranged between 17 and 36%. In most cases, diarrhea was mild and self-limiting. In the same study, the incidence of severe diarrhea necessitating administration of IV fluids was not significantly different between groups of foals treated with azithromycin-rifampin, clarithromycin-rifampin or erythromycin-rifampin. During surges of very hot weather an idiosyncratic reaction characterized by severe hyperthermia and tachypnea has been described in foals treated with erythromycin. Anecdotal reports suggest that these reactions may occasionally occur with newer macrolides as well. Administration of antipyretic drugs and placing the foal in a cool environment will treat this problem. Severe enterocolitis has also been reported in mares whose foals are being treated with erythromycin, presumably due to disruption of the mare’s normal colonic microflora following ingestion of small amounts of active drug during coprophagia or from contamination of feeders or water buckets with drug present on the foal’s muzzle.

PROGNOSIS

Prior to the introduction of the combination erythromycin-rifampin as the recommended treatment, the prognosis of *R. equi* pneumonia was poor with reported mortality rate as high as 80%. Using erythromycin and rifampin a successful outcome (as assessed by survival) in 50 (88%) of 57 foals with confirmed *R. equi* pneumonia has been reported. However, until recently there was no information on the impact of *R. equi* infections on future athletic performance. Recently, a large collaborative study involving several major veterinary hospitals was conducted in order to definitively assess the influence of prior *R. equi* pneumonia on racing performance. The records of 115 foals (49 Thoroughbreds [TB] and 66 Standardbreds [SB]) that had chest radiographs and were diagnosed with *R. equi* pneumonia based on culture of a TBA were reviewed.\(^1^8\) All cases were treated with erythromycin and rifampin between 1984 and 1994. The survival rate was significantly higher in SB (80%) than in TB (61%). Death was more likely in foals presented with respiratory distress and the non-survivors had a higher radiographic score on admission than survivors. Of the survivors 54% (for both SB and TB) had at least one racing start as opposed to 65% for the control population suggesting that horses contracting *R. equi* pneumonia as foals are slightly less likely to race. However, those foals that raced performed as well as expected.

PREVENTION

Screening

*Rhodococcus equi* pneumonia is often not recognized until it is well advanced and, therefore, difficult to treat. Even severely affected foals may appear to suckle and behave normally to a casual observer. The rationale for screening is the assumption that detecting foals in the early stages of disease along with appropriate treatment of affected foals will improve outcome. It is important to emphasize that screening methods are not diagnostic tests. A useful screening test is one in which the probability of disease is high with a positive test result (high positive predictive value) and very low with a negative test result (high negative predictive value). The higher the prevalence of disease at a given farm, the higher the positive predictive value of a given test will be. Therefore, depending on the prevalence of *R. equi* infections on a given farm, a positive result of a screening test could be a basis to perform a diagnostic test (low to moderate prevalence) or to initiate therapy (high prevalence).

A variety of screening techniques performed serially have been described, including visual inspection of foals for clinical signs of pneumonia, monitoring rectal temperatures, hematological parameters, serology, and thoracic imaging using either radiography or ultrasonography, with empiric recommendation that screening begin around 3 weeks of age. Systematic comparisons of these tests
have not been performed. Thus, a specific recommendation for any particular screening test cannot be made, and it is likely that the optimal approach for screening may vary among farms on the basis of cumulative incidence of disease, resources available for control and prevention, and preferences of the attending veterinarian(s) and farm management.

Over the past decade, control of R. equi infections at many farms where the disease is endemic has relied on early detection of subclinical pulmonary disease using thoracic ultrasonography and initiation of treatment with antimicrobial agents prior to development of clinical signs. Ultrasonography of the chest offers several advantages over other screening tests: 1) results are specific for the presence of pulmonary pathology; 2) the procedure can be performed relatively quickly for an individual foal; 3) results are available immediately; and 4) the procedure may be more sensitive than radiography for detecting lesions in their early stages of development or in certain regions where soft tissue structures are superimposed over regions of the lung. Although controlled studies are lacking periodic ultrasonography of the chest appears to have decreased mortality due to R. equi pneumonia at some farms.

However, recent double-blinded, randomized, placebo-controlled, studies documented that approximately 88% of foals with small pulmonary lesions (sum of lesion diameters [or abscess score] of 1–10 cm) recover without antimicrobial therapy. In addition, antimicrobial treatment of foals with small ultrasonographic lesions did not significantly hasten lesion resolution compared to administration of a placebo. The use of ultrasonography for screening to detect R. equi pneumonia was recently evaluated at an endemic farm with personnel and veterinarians blinded to screening results. Of 270 foals enrolled in the study, 216 (80%) developed sonographically visible pulmonary consolidation whereas only 17% of foals developed clinically apparent R. equi pneumonia. Pulmonary lesions resolved without clinically apparent illness or antimicrobial therapy in 79% of foals with ultrasonographic lesions. In the aforementioned study, the cumulative sensitivity of ultrasonography was very good (89%) but cumulative specificity was low (62%).

Because it is impossible to know which specific foals might recover spontaneously from subclinical disease, and because R. equi infections can cause severe disease, many breeding farms elect to treat all foals with ultrasonographic lesions. This approach has resulted in an increased number of foals treated for presumptive R. equi pneumonia. The temporal association between this widespread use of macrolides and rifampin as a result of ultrasonographic screening and a perceived increase in the frequency of detection of resistant isolates in the last decade suggest that this practice may not be innocuous. Emergence of widespread macrolide- and rifampin-resistance at a farm after widespread use of these drugs was instituted as part of an ultrasonographic screening program has been documented. On that particular farm, 20–40% of R. equi isolates from pneumonic foals were resistant to macrolides and rifampin. Currently, it is unknown if macrolide- and rifampin- resistance is widespread on many horse farms relying on mass antimicrobial therapy of foals with ultrasonographic lesions or if it is an isolated problem. In addition to the cost and risk for selection for resistant bacteria, unnecessary mass antimicrobial therapy of foals with pulmonary lesions might lead to development of life-threatening adverse reactions (e.g., diarrhea or hyperthermia) in some foals.

The spontaneous resolution of ultrasonographic lesions in a large proportion of foals with ultrasonographic lesions, combined with the apparent increase in macrolide- and rifampin-resistance at some farms support the need to stop the practice of mass macrolide treatment of all subclinically affected foals with ultrasonographic lesions. The goal should be to more accurately identify, of the many subclinically infected foals, which few are likely to go on to develop disease and hence require treatment. The degree of severity and the number of ultrasonographic lesions that warrant therapy are unknown and may vary by farm, geographical region, and age at which lesions are detected. Additional studies are needed to establish better criteria to determine the need for therapy in
subclinically affected foals and to better quantify the risks versus benefits of treating foals with subclinical ultrasonographic lesions.

**Passive Immunization**

Intravenous administration of HIP obtained from horses vaccinated against *R. equi* using various antigens has generally proved effective in significantly reducing the severity of *R. equi* pneumonia in foals following experimental challenge. However, studies evaluating the efficacy of various HIP preparations under field conditions have given equivocal results. Although the data are conflicting and not all trials have shown a statistically significant reduction in the cumulative incidence of *R. equi* pneumonia, 5 of 7 studies have demonstrated reduction of relative risk, suggesting some benefit of HIP.

Use of HIP licensed as an aid in the control of *R. equi* pneumonia is recommended (rather than plasma simply obtained from horses hyperimmunized against *R. equi*) because licensure ensures standard of potency, purity, and safety. Currently, there is insufficient information to recommend one brand of licensed antibody product over another.

The optimal amount of plasma to be transfused and the optimal age at which transfusion should occur remain to be determined. Administration of HIP 9 days after aerosol infection of foals with *R. equi* did not confer protection, suggesting that administration of HIP prior to infection is important. Because of evidence that many foals become infected early in life, it is commonly recommended that foals receive transfusion of at least 1 liter of HIP no later than the second day of life. Because early administration may result in the decline of passively transferred antibody to a non-protective level at a time when foals are still susceptible to *R. equi* and when environmental challenge is high, it is common practice to administer a second dose of HIP at 2–4 weeks of age.

Transfusion of HIP is not completely effective, and therefore does not eliminate the need for careful monitoring of foals at risk. In addition to being incompletely effective, transfusion of HIP carries some risk to foals, both in terms of trauma that may occur during handling and adverse reactions to transfusions. The process is also time- and labor-intensive, and expensive. The cost effectiveness of transfusion depends on the value of the foals and the prevalence of disease at a given farm.

**References**

Other Lower Respiratory Tract Disorders of the Older Foal
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INTRODUCTION
Bronchopneumonia is one of the leading causes of both morbidity and mortality in foals between 1 and 6 months of age. Foal pneumonia has a major financial impact on the horse industry. Not only does pneumonia account for significant mortality on some farms but therapy is expensive and the effect on subsequent performance of the equine athlete may be substantial if the disease is not recognized and treated early. The morbidity rate has been estimated between 6–9% across the United States. It is likely, however, that the true incidence of distal respiratory tract infection is much higher and that many cases go unrecognized and resolve spontaneously. Indeed, careful weekly physical examination of more than 200 Thoroughbred foals on 10 farms, demonstrated an average morbidity from distal respiratory tract infection of 82%. In foals, lower respiratory tract infections may be localized to the bronchi (bronchitis) or also involve the pulmonary parenchyma (pneumonia). In equine medicine, the term bronchopneumonia is often used to refer to lower respiratory tract infection regardless of whether the infection is localized to the bronchi or also involve the lung parenchyma. The spectrum of clinical signs shown by affected foals is broad and reflects the severity of the disease process. Early identification of affected foals and immediate initiation of appropriate therapy are essential to prevent mortality and functional impairment of the respiratory system.

ETIOLOGICAL AGENTS
Bacteria
Although a wide variety of microorganisms have been associated with bronchopneumonia in foals, the vast majority of cases are bacterial in origin. Bacterial bronchopneumonia in foals is generally caused by opportunistic pathogens that are normal inhabitants of the equine upper respiratory tract or gastrointestinal tract, or saprophytic environmental microorganisms. *Streptococcus equi* subspecies *zooepidemicus* (*S. zooepidemicus*) is by far the most common bacterial pathogen isolated from foals with bronchopneumonia. In a prospective study, *S. zooepidemicus* was isolated from 88% of foals with lower respiratory tract disease and was positively correlated with the percentage of neutrophils in pulmonary airway secretions. *Streptococcus equi* subspecies *equi* (strangles) infections are common in foals and young horses, but this organism is rarely isolated from the lungs of foals with bronchopneumonia. *Rhodococcus equi* pneumonia may occur sporadically or be enzootic on some farms. Non-enteric gram-negative bacteria, such as *Pasteurella* spp., *Actinobacillus* spp. and *Bordetella bronchiseptica*, are also frequently isolated, either alone or in combination with *S. zooepidemicus*. Enteric gram-negative bacteria, such as *Klebsiella* spp., *Escherichia coli*, *Salmonella* spp., may also be isolated. Other aerobic bacteria, such as *Pseudomonas aeruginosa* and *Staphylococcus* spp., are occasionally isolated. *Pseudomonas* spp. are rarely a primary cause of pneumonia in horses and their presence often reflects contamination of equipment used for taking airway samples (such as endoscopes). Anaerobic bacteria are isolated much less frequently from foals with bronchopneumonia when compared to the incidence in adult horses.

Viruses
Viral agents may predispose to secondary bacterial pneumonia by inducing ulceration of the pulmonary epithelium, reducing mucociliary clearance, and impairing alveolar macrophage function. However, with the possible exception of EHV-2, it is rarely possible to isolate a viral agent or demonstrate seroconversion by the time foals present with signs of bronchopneumonia. In one study, the rate of isolation of EHV-2 in tracheobronchial aspirates (TBA) of foals with bacterial bronchopneumonia (20/30,
66%) was significantly greater than from clinically normal foals (1/20, 5%).5 In contrast, in another study, EHV-2 or other viral agents were not isolated from TBA obtained from 101 foals with bacterial lower respiratory tract infections. (Hoffman, 1998) EHV-2 remains latent in B lymphocytes and can be isolated from the blood of approximately 80–90% of clinically healthy foals. The role of EHV-2 in development of bacterial infections of the lower respiratory tract infections in foals remains to be determined.

**Mycoplasma**

Several *Mycoplasma* species have been isolated from the respiratory tract of both diseased and healthy horses with *M. felis* and *M. equirhinis* being the most common isolates. *M. felis* has been isolated from cases of pleuropneumonia in adult horses and experimental infection with this organism induced pleuritis. (Hoffman 1992; Ogilvie 1983) *M. felis* has also been associated with outbreaks of lower respiratory tract disease in horses.6 In one study, there was an association between the presence of *Mycoplasma* spp. in the nasopharynx and respiratory disease in foals.7 In another study, *Mycoplasma* spp. were cultured from TBA obtained from only 4 of 101 foals with lower respiratory tract infection.4

**Fungi**

Molds and fungi isolated from tracheobronchial aspirates of foals are usually environmental contaminants and rarely contribute to the disease process. Opportunistic fungi, such as *Aspergillus* spp., are rare causes of severe pulmonary disease in immunocompromised patients, in foals with severe systemic diseases (most commonly enterocolitis), or in foals treated with prolonged broad-spectrum antibacterial agents.

*Pneumocystis jiroveci* (formerly *P. carinii*) lung infection develops in approximately 33% of Arabian foals with CID.8 It has also been reported in a variety of other breeds, although, in most cases, no attempt was made to assess immune function. The onset of clinical signs in affected foals ranges from a 3-week history of weakness, weight loss and nasal discharge to acute respiratory distress. Foals with *P. jiroveci* infections should be treated with trimethoprim sulfonamide combinations (30 mg/kg orally q 12 h).

**Parasitic**

Parasitic pneumonia in foals is caused either by migrating larvae of *Parascaris equorum*, or adults and larvae of *Dictyocaulus arnfieldi*. Eggs shed by *P. equorum*-infected horses mature to infective stages in 1–2 weeks. After infection, larvae appear in the liver in 2 days and in the lungs by 7–14 days.9 The larvae then travel up the bronchial tree and are swallowed. The prepatent period is 10–12 weeks. Larval migration of *P. equorum* results in eosinophilic interstitial pneumonia. Clinical signs of respiratory disease are first noted 10–13 days following experimental infection and typically last 5–10 days. Lung lesions may persist for more than 80 days postinfection.9

*Dictyocaulus arnfieldi* may cause respiratory disease in foals kept on pasture with donkeys or mules. Donkeys and mules may be asymptomatic carriers and contaminate the environment. After ingestion, infective third stage larvae penetrate the intestinal wall and travel to the lungs via the mesenteric lymphatics. Larvae reach the lungs approximately one week postinfection where they mature in peripheral bronchi.10 The parasite may be seen during bronchoscopy. In adult horses, infections are usually non-patent, whereas in foals patent infection may develop. In a patent infection, eggs are laid in the bronchi and hatch quickly so that first-stage larvae ascend by the mucociliary apparatus, are swallowed and passed in the feces. The prepatent period is 2–3 months. Fenbendazole (10 mg/kg/day for 5 consecutive days) is effective against both adult and migrating larvae of *P. equorum* and *D. arnfieldi*. Although widely reported as effective in older literature, *P. equorum* resistance to ivermectin is now widely documented.
**Epidemiology**

The highest frequency of distal respiratory tract infections occurs in foals between 1 and 6 months with a peak incidence around 4 months of age.\(^3\) The management and environmental factors associated with development of bronchopneumonia in foals have never been critically investigated. In a prospective study, shipment of foal with dam to stud, foal dystocia, IgG status as neonate, foaling location (resident farm vs. other farm) and housing type (outdoors with access to shed vs. daily turnout from stable) were not significantly associated with development of lower respiratory tract infection.\(^3\) Infection was also as likely to be detected before as after weaning.\(^3\)

**Clinical Signs and Physical Examination**

The spectrum of clinical signs ranges from an otherwise normal appearing foal with mild bilateral nasal discharge or intermittent cough to one with severe cough, profuse purulent nasal discharge, fever, anorexia, depression and respiratory distress. Mucooid to mucopurulent bilateral nasal discharge, sometimes only evidenced by crusting around the nostrils, is the most common clinical finding in foals with bronchopneumonia.\(^3\) However, the absence of nasal discharge does not rule out lower respiratory tract disease as exudate from the lungs can be swallowed and not appear as nasal discharge. Coughing is detected in approximately 50% of foals with lower respiratory tract infections. Mild tachypnea and altered respiratory character are also common features. Resting respiratory rates greater than 40 breaths per minute at rest in foals older than 3 weeks of age are usually considered abnormal and deserve further evaluation. Increased intercostal effort, often characterized by asynchronous rib excursion is a subtle but common early sign.\(^2\) Most affected foals are well grown and in good body conditions, but weight loss may become apparent with chronicity in severely affected cases. Although septicemia is not as common in older foals as it is in neonates, the examiner should be alert for other disease processes such as septic arthritis and diarrhea.

Careful auscultation after application of a rebreathing bag (if not precluded by respiratory distress) is extremely valuable in defining the presence and sometimes extent of lung involvement. In one study, abnormal lung sounds were detected in 30 of 86 (35%) foals with pneumonia whereas every affected foal had abnormal lung sounds when using a rebreathing bag.\(^3\) The bronchovesicular lung sounds of foals are much louder than that of adult horses. The lung sounds of foals with distal respiratory tract infection vary considerably and may be confused by sounds referred from the upper airway. Foals with a large amount of secretions in the trachea often have an audible and palpable tracheal rattle. Most foals with bronchopneumonia cough when the rebreathing bag is applied whereas normal foals do not. Occasional inspiratory and expiratory crackles and/or wheezes may be heard over affected areas, which are more commonly located cranioventrally. Because consolidated lung parenchyma is a good acoustic medium, mild consolidation sometimes results in only increased bronchial sounds. In contrast, the lung sounds may be diminished in areas of severe consolidation, extensive abscess formation, or pleural effusion. Pleural effusion is a rare finding in foals with bronchopneumonia.

**Diagnosis**

Diagnosis of lower respiratory tract infection is generally based on clinical signs and careful auscultation of the lungs with a rebreathing bag. The need for additional diagnostic procedures is determined by: the herd history, number and the value of the foals, severity and duration of the clinical signs, treatment used and response to therapy. On large farms, the disease process is often well advanced in the first animal(s) diagnosed, but additional foals are often affected but not yet showing clinical signs. Diagnostic evaluation should therefore be directed at the entire herd because it is unlikely that a single foal will be affected. In foals suspected of having pneumonia, the goal of diagnostic evaluation is to rule out diseases of the upper respiratory tract, and to determine the etiology and severity of lung involvement.
A complete blood count (CBC) including plasma protein and fibrinogen concentrations may reveal neutrophilic leukocytosis and/or increased fibrinogen concentrations in some affected foals. There does not seem to be a good correlation between the severity of clinical signs and the presence or magnitude of hematologic changes. In a prospective study, CBC and fibrinogen concentrations were not significantly different between foals with confirmed lower respiratory tract infection and healthy controls.\(^3\) When elevated, sequential measurement of plasma fibrinogen concentrations provides a useful means of monitoring response to treatment and is a useful guide in the decision to discontinue treatment. Persistent lymphopenia (< 1000/μl) indicates the need for further evaluation of immune function, especially in Arabian foals at risk for combined immunodeficiency. Parasitic pneumonia should be considered in foals with clinical signs of lower respiratory tract disease and peripheral eosinophilia.

A tracheobronchial aspirate (TBA) for cytologic examination and bacterial culture is the most definitive diagnostic procedure available. Whenever possible, antimicrobial therapy should be discontinued at least 24 hours before performing a tracheal wash. TBA can easily be obtained by percutaneous transtracheal aspiration or, alternatively, with a sterile polyethylene tube passed through the biopsy channel of a flexible fiber optic endoscope. Endoscopy has the advantage of allowing selective aspiration of exudate when it is present (which may therefore enhance recovery of bacteria). However, bacterial contamination of nasal or pharyngeal origin commonly occurs with endoscopy. The use of a sterile cellulose sheath over the endoscope,\(^11\) or a guarded endoscopy swab or aspiration catheter (Mila International Inc.) passed through the biopsy channel of the endoscope\(^12\) significantly reduces, but may not completely eliminate, upper airway contamination. Under field conditions, it is not always practical or even indicated to do a TBA on every pneumatic foal. A reasonable approach is to perform TBA on the first few cases during an outbreak or in cases that do not respond to appropriate antimicrobial therapy.

The trachea is not a perfectly sterile site and potentially pathogenic bacteria can be isolated from the trachea of clinically normal foals.\(^13\) Therefore culture results should always be interpreted in the context of clinical signs and cytological examination. Pulmonary alveolar macrophages and columnar ciliated epithelial cells predominate in healthy individuals. The percentage of neutrophils is quite variable in a population of apparently healthy horses but less than 40% well preserved neutrophils is usually considered normal.\(^13,14\) Occasional plant spores and fungal hyphae may be present, either free or in large mononuclear cells. Their presence does not necessarily indicate fungal infection and probably reflect the horse’s environment. If bacteria are seen in the absence of cytological evidence of sepsis, it is unlikely that they are the cause of the foal’s respiratory problem. Presence of squamous epithelial cells indicates contamination with the upper respiratory tract or pharynx and is more common in samples obtained via the endoscope.

In cases of lower respiratory tract infection, the neutrophil is the primary cell type seen and mucus is abundant. The neutrophils are degenerate (karyolysis, hypersegmented or pyknotic nuclei) and intra-or extra-cellular bacteria are often present. Presence of larvae or eosinophilic inflammation in foals is suggestive of parasitic pneumonia. Special stain techniques may be necessary to identify unusual pathogens such as *Pneumocystis jiroveci*, which is best demonstrated by a silver stain. BAL fluid is more sensitive than a tracheobronchial aspirate for the detection of *Pneumocystis jiroveci*.

Thoracic radiography and/or ultrasonography are indicated in more severe cases in which consolidation or lung abscessation is suspected. In addition to being useful for determining the severity of pneumonia, these two techniques are also useful in assessing response to therapy. Thoracic ultrasonography can be performed using a range of transducers and machine types. The normal aerated lung parenchyma is not penetrated by the ultrasound beam, rendering only the pleural space and superficial lung surface available for study. Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas, but may not be as useful as radiography to evaluate the full extent of lung lesions, since lesions with overlying aerated lung will not be detected. However, in most
foals with bronchopneumonia the periphery of the lung is affected, enabling the clinician to successfully image some of the lesions. Early ultrasonographic lesions are nonspecific and may only include irregularities of the pleural surface. These lesions may progress to form focal areas of consolidation of various sizes. Consolidated lung varies in appearance from dimples of the pleural surface to large wedge-shaped areas of sonolucent lungs.

In horses with mild, septic, inflammatory, airway disease, thoracic radiographs may be normal or only revealed mild, bronchial or bronchointerstitial patterns. In more severely affected animals, radiographs demonstrate irregular opacities in the ventral thorax that may obscure the normal vasculature and cardiac silhouette. Air bronchograms are sometimes visible. Abscesses are often present as circular, soft-tissue, opacities of varying sizes. In some cases they may be cavitated with thick walls and a distinct, horizontal line representing fluid-gas interface. Pleural effusion is rare in foals with bronchopneumonia, but when present, it appears as a horizontal line demarcating a ventral, soft-tissue opacity that obscures the heart and ventral lung fields. Although ultrasonography is more convenient than radiography, the latter should still be performed, when possible, to detect and monitor resolution of deep pulmonary abscesses that may be missed during ultrasonography.

Upper-airway endoscopy is useful to rule out upper-airway infection when physical examination and auscultation of the lungs is not conclusive. Presence of mucopurulent secretions in the trachea and bronchi in foals is suggestive of a bacterial infection of the lower respiratory tract. Other procedures that may be useful in the diagnostic evaluation of foals with lower respiratory tract infection include arterial blood gas analysis to evaluate oxygenation and ventilation in severely affected foals, blood cultures, virus isolation, PCR testing for respiratory viruses, serology (paired samples) for respiratory viruses, fecal flotation, and Baermann test on feces when parasitic pneumonia is suspected.

**Therapy**

The goal of therapy is to kill or inhibit bacterial pathogens, improve respiratory function, minimize stress, and maximize patient comfort and environmental quality. Restricting exercise is important in severely affected cases to limit ventilatory demand. In milder or resolving cases, limited exercise may facilitate expectoration. Affected foals should be kept in a cool, clean and well-ventilated environment.

**Antimicrobial Therapy**

Administration of antimicrobial agents is the most important part of the therapeutic plan. The choice of the antimicrobial agent depends on the severity of the clinical signs, cost, ease of administration, experience within the herd and, when available, results of bacteriologic culture and susceptibility testing of a TBA. Since a high percentage of pneumonia in foals older than 1 month is caused by bacteria with a predictable susceptibility profile such as *S. zooepidemicus* and *Pasteurella* ssp. (this is not true for neonatal foals), ceftiofur (2.2–4.4 mg/kg q 12–24 h IM) is often used for initial therapy on farms where *R. equi* is not enzootic. Ceftiofur, a third generation cephalosporin, has a broad spectrum of activity that includes most of the etiologic agents of foal pneumonia, except *R. equi*. A single daily dose of ceftiofur sodium at 2.2 mg/kg IM or the label dose of ceftiofur crystalline free acid is usually sufficient to maintain serum concentrations above the minimum inhibitory concentration (MIC) of *S. zooepidemicus*. Procaine penicillin G or ampicillin is also highly effective against *S. zooepidemicus*. If resistant gram-negative organisms are present, aminoglycosides (gentamicin or amikacin) are often combined with penicillin. Trimethoprim-sulfonamide (TMS) combinations are attractive because they can be administered orally and for long periods of time. Unfortunately, the usefulness of TMS combinations for the treatment of bacterial respiratory tract infections in foals is limited by its lack of *in vivo* activity against *S. zooepidemicus*.

The therapeutic regimen should be reevaluated if the foal does not show clinical improvement within 3 to 5 days following initiation of therapy. Chronic cases generally respond more slowly than do
acute cases. Treatment should be continued for a minimum of 10 days, and much longer in severe cases. Clinical signs, lung auscultation, measurement of fibrinogen concentrations, and imaging techniques (ultrasonography, radiography) can be used to assess efficacy and determine duration of therapy. Significant reduction in the frequency and number of S. zooepidemicus isolated during therapy supported a causal role for this microorganism in development of lower respiratory tract infection. In contrast, the frequency of \(-\)hemolytic streptococci, Staphylococcus epidermidis and Streptomyces spp. increased during treatment suggesting a commensal or competitive role for these microorganisms.\(^\text{15}\)

Most cases make a complete recovery if diagnosed early and treated appropriately. In a prospective study involving 178 foals with lower respiratory tract infection, complete resolution of the clinical signs was observed during the treatment period in all but 7 (4\%) of cases.\(^\text{15}\) In the same study, the relapse rate of lower respiratory infections was approximately 30\%. Relapses were identified from 7 to 35 days after discontinuation of therapy. Relapse was not associated with development of resistant organisms.

Aerosolized antimicrobial agents may be a useful adjunct to oral or systemic administration particularly in foals with chronic septic inflammatory airway disease and no or minimal involvement of the lung parenchyma. Aerosol administration of antimicrobial agents can result in high drug concentrations in the respiratory tract while minimizing systemic concentrations and their resulting toxicity.\(^\text{16}\) Antimicrobial delivery by inhalation is greatly influenced by the product formulation and type of nebulizer. In one study, the particle size distribution and particle density of gentamicin sulfate and ceftiofur sodium aerosols were affected by the antimicrobial concentration of the solution.\(^\text{17}\) Gentamicin solutions at a concentration of 50 mg/mL or ceftiofur solutions at a concentration of 25 mg/mL produced the optimal combinations of particle size and aerosol density when using a medical ultrasonic nebulizer.\(^\text{17}\) The major limitation to the use of aerosolized gentamicin in horses is its lack of activity against S. zooepidemicus, the most common bacterial pathogen of the equine respiratory tract. In contrast, ceftiofur is active against virtually all S. zooepidemicus isolates. Aerosolized antimicrobial agents should be considered in cases that do not respond to systemic antimicrobial agents or cases that relapse following appropriate therapy.

Other Therapies
Nursing care, provision of adequate nutrition and hydration, and maintaining foals in a cool and well-ventilated environment are also important. Oxygen therapy using humidified oxygen by pharyngeal insufflation in moderately hypoxemic foals (PaO\(_2\) < 65 mm Hg), or by percutaneous transtracheal oxygenation in severely hypoxemic animals (PaO\(_2\) < 50 mm Hg)\(^\text{18}\) is indicated in foals with persistent hypoxemia or cyanosis. Nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine (1.1 mg/kg IV or PO q 12h) may minimize the damaging effects of the cyclooxygenase-derived inflammatory mediators and are of value in reducing fever and improving attitude and appetite in febrile depressed anorectic foals. The use of bronchodilators in treating foal pneumonia is usually not rewarding since bronchoconstriction represents a relatively small part of the overall lung pathology. Nevertheless rare foals with severe bronchopneumonia and a positive bronchodilator response test with inhaled albuterol may benefit from inhaled bronchodilators.

REFERENCES


Update on Infections Caused by *Lawsonia intracellularis* in Foals
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**INTRODUCTION**

*Lawsonia intracellularis*, a gram-negative obligate intracellular pathogen, is the causative agent of proliferative enteropathy. The microorganism resides freely within the apical cytoplasm of infected enterocytes, resulting in hyperplasia of the affected enterocyte and subsequent malabsorption. Proliferative enteropathy is a transmissible disease with worldwide distribution that affects a multitude of animal species. The disease is endemic in swine and has been studied extensively in that species. Since the first report of proliferative enteropathy in foals in 1982, multiple isolated reports and outbreaks have been described on breeding farms.\(^1\)\(^2\) This manuscript reviews the clinical manifestation, diagnosis, treatment and prevention of proliferative enteropathy in foals with particular emphasis on recent developments.

**CLINICAL PRESENTATION**

The disease primarily affects foals between 3 and 9 months of age, although there are occasional reports in older horses.\(^1\)\(^3\) The disease is more common in the fall (September to December), which might just be a consequence of the age of susceptibility to the disease.\(^1\) The clinical signs associated with proliferative enteropathy in foals include subcutaneous edema, depression, diarrhea, fever, and colic. In some foals, the only clinical abnormality is lower daily weight gains compared to unaffected pasture mated. Subclinical infection is also common. In a retrospective case series of 57 foals with proliferative enteropathy, the most common clinical signs were ventral edema (46/57), lethargy (18/57), diarrhea (15/57), fever (11/57), and colic (4/57).\(^1\) The clinical picture may be complicated by concurrent diseases.

Clinical signs of foals with proliferative enteropathy are similar to those of foals with other diseases that can cause failure to thrive and protein loosing enteropathy such as parasitism, gastroduodenal ulcers, sand impaction, NSAIDs toxicity, and infectious agents implicated in weanling diarrhea. These infectious agents include *Salmonella*, *Rhodococcus equi*, *Clostridium* spp., *Neorickettsia risticii*, and rotavirus.

**DIAGNOSIS**

Antemortem diagnosis of proliferative enteropathy is based on clinical signs, presence hypoalbuminemia, and exclusion of the other common enteric conditions listed above. Detection of thickening of one or multiple segments of the small intestine by ultrasonography further supports the diagnosis. However, failure to identify thickened small intestine does not rule out proliferative enteropathy. Similarly, small intestinal thickening is not necessarily pathognomonic for proliferative enteropathy and can be seen occasionally with other diseases such as salmonellosis or clostridiosis. Detection of *L. intracellularis* DNA by PCR in fecal samples or fecal swabs from foals with hypoalbuminemia supports the diagnosis of proliferative enteropathy.\(^1\)\(^4\) However, this test has low sensitivity and a negative result does not rule out proliferative enteropathy. In one report, 38 of 51 (75%) foals with proliferative enteropathy tested positive by fecal PCR.\(^1\) In the same study, 38 of 41 (93%) foals with proliferative enteropathy were tested positive for serum antibody against *L. intracellularis* suggesting that serology is more sensitive than fecal PCR.\(^1\) However, serology detects previous exposure and does not necessarily indicate current infection. The preferred serological test is the immunoperoxidase monolayer assay (IPMA) although slide-based immunoperoxidase assays and some ELISAs may also provide adequate results.\(^5\) Many healthy weanlings become seropositive for *L. intracellularis* even on farms with no history of clinical cases of proliferative enteropathy.\(^6\) Therefore,
positive serology, in the absence of hypoalbuminemia, should not be used as a reason to initiate therapy.

Definitive diagnosis of proliferative enteropathy is obtained based on the presence of the microorganism within the apical cytoplasm of proliferating epithelial cells. Microorganisms can be detected using silver stain, immunohistochemistry, or molecular approaches such as PCR. Lesions are characterized by hyperplasia of the intestinal crypts which often causes grossly detectable thickening of the mucosa of the jejunum or ileum. Occasionally, the duodenum or large intestine may also be affected.

**TREATMENT**

Because *L. intracellularis* is an obligate intracellular pathogen, therapy should include an antimicrobial agent with good intracellular penetration. Pleuromutilins (tiamulin, valnemulin), macrolides (erythromycin, tylosin, tilamcosin), carbadox, and fluoroquinolones (enrofloxacin, difloxacin) are active against most isolates of *L. intracellularis* in *in vitro* intracellular and extracellular assays.\(^7\,^9\) To a lesser extent, tetracyclines, lincosamides, ampicillin, and penicillin are also active *in vitro*.\(^7\,^9\) Antibiotic agents commonly used in foals with proliferative enteropathy include a macrolide (azithromycin [10 mg/kg PO q 24 h], clarithromycin [7.5 mg/kg q 12 h], or erythromycin [25 mg/kg q 8 h]) alone or in combination with rifampin (5 mg/kg q 12 h), oxytetracycline (6.6 mg/kg slowly IV q 24 h), doxycycline (10 mg/kg PO q 12 h), or chloramphenicol (50 mg/kg PO q 6 h).\(^1^3\,^10,^11\) There are no studies comparing the relative efficacy of these antimicrobial agents for the treatment of proliferative enteropathy in foals. Therapy is typically administered for 2–4 weeks.\(^3\)

Additional supportive therapy may be indicated in some severely affected foals. Foals that are anorectic may require enteral or parenteral nutritional support. Foals with severe diarrhea may require judicious administration of intravenous fluids to maintain hydration. When fluid therapy is indicated, it is important that crystalloids IV fluids are administered judiciously because hypoalbuminemic foals are predisposed to develop pronounced edema. Foals with very severe hypoalbuminemia may benefit from administration of plasma or synthetic colloids. Surgical exploration may be warranted in foals with recurrent colic or in foals that fail to respond to long-term therapy with appropriate antimicrobial agents. In some cases, resection of focally affected small intestine in combination with antimicrobial therapy has led to a favorable outcome.\(^12\)

**PROGNOSIS**

With appropriate antimicrobial therapy, the prognosis for survival is good. In several case series, the proportion of survivors has ranged between 80% and 93%.\(^1^3,^10\) A rapid improvement in attitude, improvement, and appetite may be observed in some foals. However, resolution of hypoalbuminemia is slow. In many cases, the prognosis may be confounded by concurrent diseases.

**PREVENTION**

**Screening**

Studies have shown that the rate of exposure to *L. intracellularis* is higher than the clinical attack rate.\(^6\) When a foal from a given farm is diagnosed with proliferative enteropathy, it is likely that many foals at the same farm have been exposed and may have subclinical infection. Therefore, screening herd mates for exposure and subclinical disease is advised.\(^1^1\) Herd exposure can be assessed by IPMA. Although serology using IPMA will provide useful data regarding exposure at the farm level, a positive IPMA on a given foal in the absence of hypoproteinemia or clinical signs only indicates past exposure and should not be perceived as evidence for therapy. Daily clinical monitoring of herd mates is recommended to identify early clinical signs of disease. The most economical mean of detecting subclinical disease is to measure total protein concentration by refractometry. A more accurate, but also more expensive
Ileitis, resulted in spontaneous clinical cases of hypoproteinaemia (total protein < 5 g/dL) or hypoalbuminemia (< 3.0 mg/dL) should undergo additional diagnostic testing to determine if *L. intracellularis* is the likely cause of hypoproteinaemia (e.g., serology and fecal PCR) and to rule out other causes of hypoproteinaemia.

The approach for monitoring a herd endemic for proliferative enteropathy is similar. This includes daily clinical monitoring of foals and monthly monitoring for hypoproteinaemia or hypoalbuminemia. Monitoring should begin 4 weeks prior the earliest month in which clinical cases have been documented on the farm. Doxycycline at 10 mg/kg PO for 2 weeks has been recommended for the treatment of foals with severe hypoproteinaemia or hypoalbuminemia from subclinical infection. In some cases, spontaneous resolution has occurred without antimicrobial therapy. The proportion of subclinically affected foals that recover without antimicrobial treatment is unknown and may vary from farm to farm. Clinical or subclinical cases of proliferative enteropathy should be separated from the rest of the herd until fecal shedding has ceased to decrease environmental contamination. Maintaining good pest control and preventing wild and non-equine domestic animal species to gain access to feed might minimize the risk of exposure to *L. intracellularis*.

**Immunization**

A live attenuated vaccine is available for the prevention of proliferative enteropathy in pigs (Enterisol L. L. ileitis, Boehringer Ingelheim, St Joseph, MO). This vaccine has been shown to be safe and immunogenic when administered to foals. Intrarectal administration of 30 mL of the vaccine twice 30 days apart resulted in complete protection against subsequent challenge with virulent *L. intracellularis*. The same vaccination protocol has been tested under field conditions on endemic farms with historical prevalence of proliferative enteropathy of at least 10%. Only 1 of 96 vaccinated foals and 3 of 106 non vaccinated foals developed proliferative enteropathy. Due to the low disease incidence, the true efficacy of the vaccine could not be determined. Immunization of foals should be considered on endemic farms. Timing of vaccination must be determined based on the expected onset of clinical disease on the farm.

**References**

Scientific Basis & Clinical Applications of Veterinary Medical Acupuncture
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INTRODUCTION
There has been a great increase in interest in veterinary acupuncture recently, both by the public and the veterinary medical community. With this increased awareness, there has been an increase in research and thus a better understanding of its physiologic basis and its clinical applications.

No one theory on the physiologic basis of acupuncture explains all the physiologic effects. Acupuncture produces multiple physiologic effects that appear to activate the body’s homeostatic regulatory mechanisms. In addition to pain inhibition, others have looked more widely to consider the effects of acupuncture on the control of the cardiovascular and respiratory systems and the neuroimmunologic axis. As methods of histochemical and electrophysiologic data acquisition become more sophisticated, additional neurophysiologic mechanisms, as well as confirmation or refutation of current ones, will add to our understanding of pain perception and modulation. Currently, functional MRI is providing new information on the correlation between acupuncture points and the activation of specific regions of the brain. Future research will hopefully lead to a comprehensive understanding of the effects of acupuncture.

SCIENTIFIC BASIS
Acupuncture (AP) may be defined as the stimulation of specific predetermined points on the body to achieve a therapeutic or homeostatic effect. Acupuncture points are areas on the skin of decreased electrical resistance or increased electrical conductivity. Acupuncture points correspond to four known neural structures. Type I acupoints, which make up 67% of all acupoints, are considered motor points. The motor point is the point in a muscle, which, when electrical stimulation is applied, will produce a maximal contraction with minimal intensity of stimulation. Motor points are located near the point where the nerve enters the muscle. Type II points are located on the superficial nerves in the sagittal plane on the midline dorsally and ventrally. Type III acupoints are located at high-density foci of superficial nerves and nerve plexuses. For instance, acupoint GB-34 is located at the point where the common peroneal nerve divides into the deep and superficial branches. Type IV acupoints are located at the muscle tendon junctions where the Golgi tendon organ is located. Recently, histologic studies have revealed that small microtubules consisting of free nerve endings, arterioles and venules penetrate through the fascia at acupuncture points. Based on this histologic evidence they have also been called neurovascular nodes.

Acupuncture has many varied physiologic effects on all systems throughout the body. No one mechanism can explain all the physiologic effects observed. The traditional Chinese medical theories have explained these effects for four thousand years based upon empirical observations and descriptions of naturally occurring phenomena. The traditional Chinese medical theories include: the five element theory and the theory of eight principles. Scientific research has been able to document many of these effects. The western medical theories include the gate and multiple gate theories, autonomic theories, humeral mechanisms as well as the bioelectric theories. The neural non-opiate or gate theory attempts to explain the analgesic effects of acupuncture. It involves the interaction of inhibitory interneurons on pain transmitting neurons. Recent reviews of the latest research on the neurophysiologic effects of acupuncture are available.

The neural opiate theory is based on evidence that acupuncture stimulates the release of endogenous opiates, endorphins and encephalins. This mechanism acts at several levels in the central nervous system to inhibit pain perception in higher centers and to inhibit pain transmission from the spinal cord via descending inhibition. The hormonal opiate theory involves the interaction of neurons
with the subsequent release of humoral factors from the hypothalamic-pituitary axis. Acupuncture facilitates the function of the neuroendocrine system and has been found to have effects on ovarian, testicular, thyroid, parathyroid and pancreatic function. Through its effects on the neuroendocrine system and its homeostatic regulatory functions it has been found to affect blood pressure, pulse, respiration, gastrointestinal motility, hormone secretion, leukocyte production and accelerate the healing process.

Many of our somatovisceral reflexes may be explained through the autonomic theories of acupuncture. Cutaneous needle stimulation is transmitted to the internal viscera through the somatovisceral neuronal synapses in Laminae I & V of the spinal cord.

Essentially, acupuncture stimulates various sensory receptors (pain, thermal, pressure, touch) which stimulates sensory afferent nerves which transmit the signal through the central nervous system to the hypothalamic-pituitary system. Various neurotransmitters and neurohormones are then released and have their subsequent effects throughout the body. A detailed description of the physiologic basis of acupuncture is reviewed by Steiss.

An additional theory, The Liquid Crystalline Collagen Continuum Theory of Acupuncture has been proposed. This theory integrates all previous theories from the Traditional Chinese Medical Theories (TCM) along with the bioelectrical theories, Gate theory, neural opiate and nonopiate theories. It explains all of the effects of acupuncture and the speed of effects throughout the entire body.

Dr. Ho and Dr. Knight propose that the acupuncture system and the DC body field detected by Western scientists both inhere in the continuum of liquid crystalline collagen fibres that make up the bulk of the connective tissues. Bound water layers on the collagen fibres provide proton conduction pathways for rapid intercommunication throughout the body, enabling the organism to function as a coherent whole. This liquid crystalline continuum mediates hyperreactivity to allergens and the body’s responsiveness to different forms of subtle energy medicine. It constitutes a “body consciousness” working in tandem with the “brain consciousness” of the nervous system. They review supporting evidence from biochemistry, cell biology, biophysics and neurophysiology, and suggest experiments to test our hypothesis.

Drs Ho and Knight suggest that connective tissues may also be largely responsible for the rapid intercommunication that enables our body to function effectively as a coherent whole, and are therefore central to our health and well-being. The clue to the intercommunication function of connective tissues lies in the properties of collagen, which makes up 70% or more of all the protein of the connective tissues. Connective tissues, in turn form the bulk of the body of most multicellular animals.

Drs Ho and Knight therefore have proposed that the acupuncture (meridian) system and the DC body field detected by Western scientists both inhere in the continuum of liquid crystalline collagen fibres and the associated layers of bound water that make up the bulk of the connective tissues of the body. Acupuncture meridians may be associated with the bound water layers along oriented collagen fibres, which provide proton conduction pathways for rapid intercommunication throughout the body; while acupuncture points may correspond to gaps in the fibres or fibres oriented at right angles to the surface of the skin. The sum total of the electrical and electromechanical activities of the liquid crystalline continuum constitutes a “body consciousness” that works in tandem with the “brain consciousness” of the nervous system. We have reviewed supporting evidence from biochemistry, cell biology, biophysics and neurophysiology.

TECHNIQUES AND INSTRUMENTATION

There are numerous techniques to stimulate acupuncture points. The following modes of stimulation are commonly used in veterinary acupuncture: dry needle stimulation, electroacupuncture,
aquapuncture, moxibustion, laser stimulation, gold implants and acupressure. Each method has its indications and limitations. Details of these techniques are described by Altman.\textsuperscript{6}

Acupuncture point selection is based on locating points on the body where stimulation will produce a beneficial change in the central nervous system by modulating ongoing physiologic activity. The number of treatments required depends upon the condition treated and the chronicity of the problem. The length of treatment varies from 5 to 30 minutes.

Acupuncture has been found to be beneficial therapeutically in the treatment of various musculoskeletal, gastrointestinal, neurological, reproductive and respiratory conditions in veterinary practice. Musculoskeletal conditions that may benefit from AP include chronic degenerative joint disease, nonsurgical cervical and thoracolumbar disc disease, immune-mediated myopathies, trigger point patterns and soft tissue injuries.\textsuperscript{7} Neurological conditions treatable with AP include nerve paralysis, epilepsy, coma, cerebrovascular accidents, various neuropathies, neuritis and neurogenic deafness.\textsuperscript{8} AP may be beneficial in the treatment of most immune-mediated conditions via its immunomodulatory effects, both stimulating or suppressing immune responses.\textsuperscript{9} Cardiovascular conditions, such as cardiac and respiratory depression and arrest, shock, arrhythmias and congestive heart failure, may benefit from AP as an adjunctive therapy.\textsuperscript{10} AP has a normoregulatory effect on GI motility, thereby being an excellent adjunct to the treatment of any vomiting or diarrhea.\textsuperscript{11} It also can be of benefit in the treatment of pancreatitis and various hepatopathies. AP can help with various reproductive disorders through its neurohormonal regulatory effects.\textsuperscript{12} AP is also being used as an excellent perioperative and postoperative analgesic therapy.\textsuperscript{13} Acupuncture does not just relieve the pain and mask a problem but actually may accelerate the healing process, restore homeostasis and resolve many conditions through its normoregulatory effects.

Acupuncture is an exciting new (yet ancient) diagnostic and therapeutic technique that one can incorporate into a conventional veterinary practice. It offers an additional approach to diagnostic and therapeutic dilemmas that may not have adequate answers based on conventional western medicine. It may also be of benefit when conventional medicine and surgery are not available.

Further research will continue to explain the physiologic basis of acupuncture. Acupuncture will continue to be incorporated into veterinary practice as an additional complementary therapy and as an adjunct to our therapeutic armamentarium as we develop a further understanding its mechanisms of action. The latest textbook on veterinary acupuncture offers comprehensive descriptions and references on all aspects of veterinary acupuncture.

REFERENCES


Introduction to the Most Commonly Used Acupuncture Points in Small Animal Veterinary Acupuncture Practice
Allen M. Schoen, MS, DVM, PhD (hon.)
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These notes described some of the most commonly used acupuncture points. By no means is this an exhaustive list. There are well over 365 acupuncture points located throughout the body. Physical anatomic similarities and variations exist in different species. The most commonly used acupuncture points for beginners are presented. Their anatomic location, physiologic actions and clinical applications are reviewed. These descriptions are taken from the Canine Acupuncture Atlas. A more comprehensive list is available in the Canine Acupuncture Atlas chapter in the text, “Veterinary Acupuncture, Ancient Art to Modern Medicine” that these notes were excerpted from. Information concerning these points is mainly transposed from human acupuncture; however, knowledge of traditional veterinary acupuncture and knowledge gained from Western small animal acupuncture practices are incorporated.

The points are listed according to the meridian numbering system, but the traditional Chinese pinyin names and their meanings are included to offer additional reference and nuance of points. The meridians are named after internal organs or TCM terms. In TCM, meridians are perceived as a complex network of major channels and their collaterals. Most acupuncture points are found along meridians and are labeled as meridian points. Not every point on a particular meridian is related to the organ or term that it is called. It is a terminology that has been adopted by the World Health Organization and accepted in the human acupuncture world and extrapolated over to veterinary medicine that has been translated from the TCM terminology. In addition, there are extra meridian points that do not belong to any meridian. Ah shi points are transient sensitive spots. Their locations may or may not correspond with locations of known acupoints. Sometimes these are also known as trigger points.

There are 12 major bilaterally distributed meridians, each with a set of meridian points. The 12 major meridians are named after various internal organs or TCM concepts. They are called: Lung (LU), Heart (HT), Pericardium (PC), Large Intestine (LI), Small Intestine (SI), Triple Heater (TH), Stomach (ST), Urinary Bladder (BL), Gallbladder (GB), Spleen (SP), Kidney (KI), Liver (LV). In addition, there are eight extra channels that are not directly associated with visceral organs. Among these are the unpaired midline channels called the Conception Vessel (CV) on the ventral midline and the Governing Vessel (GV) on the dorsal midline.

Acupuncture points are normally located in depressions between muscles, tendons and bones. They are normally palpable depressions. Acupoints are commonly found along pathways of major peripheral nerves and their superficial branches, such as the radial, median and ulnar nerves. Acupoints often appear at the site where cutaneous nerves emerge from deep fascia. Acupoints on the head are found at sites where nerves emerge from bony foramina, such as the supraorbital and infraorbital foramina. Other acupoints are found superficial to motor points, such as the location of the deep radial nerve on the long extensor muscle.

Most acupoints on the head, neck, trunk and proximal portions of the limb are used to treat local problems. However, points found distal to the elbow and stifle joints are used not only for treatment of regional discomfort, but also for treatment in remote areas. For example, the point ST-36 in the leg is used to treat problems of hind limb as well as those from abdomen to the head. ST-36 is considered one of the four master points along with SP-6. Acupuncture points are normally located in depression between muscles, tendons and bones. They are normally palpable depressions. Acupoints are commonly found along pathways of major peripheral nerves and their superficial branches, such as the radial, median and ulnar nerves. Acupoints often appear at the site where cutaneous nerves emerge from deep fascia. Acupoints on the head are found at sites where nerves emerge from bony foramina, such as
the supraorbital and infraorbital foramina. Other acupoints are found superficial to motor points, such as the location of the deep radial nerve on the long extensor muscle. LI-4 and LI-11.

A comprehensive description of the anatomy, physiology and TCM concepts of acupuncture points is described in the chapter “Anatomy and Classification of Acupoints” in the textbook of Veterinary Acupuncture, Ancient Art to Modern Medicine. Under the name of each point is information concerning the anatomic location and cutaneous nerve innervation of the point, brief information on needle insertion, and therapeutic indications. In each figure some anatomic landmarks are identified to assist in localization of the acupoints.

**Acupoints of the Thoracic Limb**

**LI-4. He Gu, union valley (Fig. 9-3)**  
Source point, master point  
Location: Between the first and second metacarpal bones, at the level of the head of the first metacarpus.  
Innervation: First dorsal common digital nerve  
Method: Perpendicular insertion 0.5 cm  
Indications: Skin disorders, pain in the head and neck, pain in the forelimb and shoulder, acupuncture analgesia, neurodermatitis. An important analgesic point.

**LI-11. Qu Chi, pond on the curve (Fig. 9-5)**  
He point, tonification point  
Location: At the lateral end of the cubital fossa when the elbow joint is flexed at a right angle, the point is at the midpoint between the tendon of the biceps brachii and the lateral epicondyle of the humerus.  
Innervation: Supplied by the cranial cutaneous antebrachial nerve. The superficial radial nerve is deep to this point. Method: Perpendicular insertion 1 to 2 cm.  
Indications: Pain in the elbow and forelimb, neurodermatitis, skin disorders, endocrine disorders. Homeostatic and immune enhancing point. Often used in allergic and infectious disorders. Important tonification point.  
Indications: Apoplexy, heatstroke, vomiting, elbow pain.

**PC-6. Nei Guan, inner pass (Fig. 9-2)**  
Connecting point to the Triple Heater meridian, confluent point to the Yin Wei channel  
Location: In the muscle groove caudal to the flexor carpi radialis and cranial to the superficial digital flexor muscles, approximately 1/6 from the carpus to the cubital fossa. Under the point is the median nerve and artery. Or 2 Cun* above the transverse crease of the wrist, between the tendons of the flexor digitorum superficialis and flexor carpi radialis.  
Innervation: Medial and lateral cutaneous antebrachial nerves. Location of this point approximates the site used in blocking the median nerve  
Method: Perpendicular insertion 0.5 to 1 cm.  
Indications: Cardiovascular disorders, neurosis, epilepsy. Disorders of the cranial abdomen, gastric ulcers, gastritis, vomiting, stomach upset. Important distal point.

**Acupoints of the Head, Trunk and Pelvic Limb**

Indication: Pain and arthritis of the stifle joint, patellar subluxation

**ST-36. Zu San Li, leg 3 miles (Figs. 9-8, 9-9)**  
He point, master point, tonification point
Location: Three-sixteenths the distance from the point ST-35 to cranial tarsus or three Cun below ST-35, about one digit breadth lateral to the tibial crest, in the lateral portion of the cranial tibial muscle. The point is known as Hou San Li (hindlimb 3 miles) in traditional veterinary acupuncture.

Innervation: Branches from the saphenous nerve. Method: Perpendicular insertion 1 to 2 cm. Indications: Gastrointestinal disorders, general tonification point for any weak condition, paralysis of the pelvic limb, endocrine and metabolic diseases, acupuncture analgesia.

**BL-11. Da Shu, big shuttle (Fig. 9-11)**

Influential point for bone

Location: In a depression 1.5 Cun lateral to the caudal border of the spinous process of the first thoracic vertebra, midpoint between the spinous process and the medial border of the scapula.

Innervation: Cutaneous branch of the dorsal ramus of the first thoracic nerve.

Method: Angular insertion medially 0.5 to 1 cm.

Indications: Rheumatoid arthritis, cervical spondylosis, cervical disk disease, forelimb pain.

**BL-13. Fei Shu, Lung association point (Fig. 9-11)**

Location: Lateral to the caudal border of the spinous process of the third thoracic vertebra, along the longitudinal line of the costal tubercula. The point is approximately midway between the midsagittal plane and the medial border of the scapula.

Innervation: Lateral branch of the dorsal ramus of the third thoracic nerve.

Method: Angular insertion medially 0.5 to 1 cm. Be careful not to cause pneumothorax.

Indications: Pneumonia, bronchitis, asthma.

**BL-14. Jue Yin Shu, Pericardium association point (Fig. 9-11)**

Location: Lateral to the caudal border of the spinous process of the fourth thoracic vertebra, along the longitudinal line of the costal tubercula. The point is approximately midway between the midsagittal plane and the medial border of the scapula.

Innervation: Lateral branch of the dorsal ramus of the fourth thoracic nerve.

Method: Angular insertion medially 0.5 to 1 cm. Be careful not to create pneumothorax.

Indications: Myocarditis, pericarditis, cough.

**BL-15. Xin Shu, Heart association point (Fig. 9-11)**

Location: Lateral to the caudal border of the spinous process of the fifth thoracic vertebra, along the longitudinal line of the costal tubercula.

Innervation: Lateral branch of the dorsal ramus of the fifth thoracic spinal nerve.

Method: Angular insertion medially 0.5 to 1 cm. Be careful not to create pneumothorax.

Indications: Heart disorders, syncope, epilepsy.

**BL-16. Du Shu, Governing Vessel association point (Fig. 9-11)**

Location: Lateral to the caudal border of the spinous process of the sixth thoracic vertebra, along the longitudinal line of the costal tubercula.

Innervation: Lateral branch of the dorsal ramus of the sixth thoracic spinal nerve. Method: Angular insertion medially 0.5 to 1 cm. Be careful not to create pneumothorax.

Indications: Myocarditis, pericarditis, abdominal pain.

**BL-17. Ge Shu, Diaphragm association point (Fig. 9-11)**

Influential point for Blood

Location: Lateral to the caudal border of the spinous process of the seventh thoracic vertebra, along the longitudinal line of the costal tubercula.

Innervation: Lateral branch of the dorsal ramus of the seventh thoracic spinal nerve. Be careful not to create pneumothorax.
Method: Angular insertion medially 0.5 to 1 cm.
Indications: Chronic hemorrhagic diseases, spasm of the diaphragm, blood dyscrasia, bronchial asthma.

**BL-18. Gan Shu, Liver association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the tenth thoracic vertebra, along the longitudinal line of the costal tubercula.
   Innervation: Lateral branch of the dorsal ramus of the tenth thoracic spinal nerve.
   Method: Angular insertion medially 0.5 to 1 cm. Be careful not to create pneumothorax.
   Indications: Liver and gallbladder problems, conjunctivitis.

**BL-19. Dan Shu, Gallbladder association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the eleventh thoracic vertebra, along the longitudinal line of the costal tubercula.
   Innervation: Lateral branch of the dorsal ramus of the eleventh thoracic spinal nerve.
   Method: Angular insertion medially 0.5 to 1 cm.
   Indications: Liver and gallbladder disorders. Local point for lumbar intervertebral disk disease.

**BL-20. Pi Shu, Spleen association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the twelfth thoracic vertebra, along the longitudinal line of the costal tubercula.
   Innervation: Lateral branch of the dorsal ramus of the twelfth thoracic spinal nerve. Method: Angular insertion medially 0.5 to 1 cm.
   Indications: Digestive disorders, pancreatic disorders, pancreatitis, vomiting, anemia. Local point for intervertebral disk disease.

**BL-21. Wei Shu, Stomach association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the thirteenth thoracic vertebra, along the longitudinal line of the costal tubercula.
   Innervation: Dorsal cutaneous branch of the thirteenth thoracic spinal nerve.
   Method: Angular insertion 0.5 to 1 cm.
   Indications: Vomiting, gastritis, gastric ulcers, pancreatitis. Local point for intervertebral disk disease.

**BL-22. San Jiao Shu, Triple Heater association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the first lumbar vertebra, along the longitudinal line of the thoracic costal tubercula.
   Innervation: Dorsal cutaneous branch of the first lumbar spinal nerve. Method: Perpendicular insertion 1 cm.
   Indications: Indigestion, dysentery, vomiting, endocrine disorders, lower back pain.

**BL-23. Shen Shu, Kidney association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the second lumbar vertebra, along the longitudinal line of the thoracic costal tubercula.
   Innervation: Dorsal cutaneous branch of the second lumbar spinal nerve. Method: Perpendicular insertion 1 to 3 cm.
   Indications: Renal disorders, urogenital disorders, back pain, vertebral spondylosis, coxofemoral arthritis, intervertebral disk disease.

**BL-24. Qi Hai Shu, sea of Qi association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the third lumbar vertebra, along the longitudinal line of the thoracic costal tubercula.
Innervation: Dorsal cutaneous branch of the third lumbar spinal nerve.
Method: Perpendicular insertion 1 to 2 cm.
Indications: Constipation, back pain, cystitis.

**BL-25. Da Chang Shu, Large Intestine association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the fifth lumbar vertebra, along the longitudinal line of the thoracic costal tubercula.
Innervation: Dorsal cutaneous branch of the fifth lumbar spinal nerve. Method: Perpendicular insertion 1 to 2 cm.
Indications: Gastrointestinal disorders: constipation, diarrhea, chronic colitis. Local point for thoracolumbar disk disease and back pain.

**BL-26. Guan Yuan Shu, enclosed original energy (Qi) association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the sixth lumbar vertebra, along the longitudinal line of the thoracic costal tubercula.
Innervation: Dorsal cutaneous branch of the sixth lumbar spinal nerve.
Method: Perpendicular insertion 0.5 to 1 cm.
Indications: Constipation, diarrhea, indigestion, lower back pain.

**BL-27. Xiao Chang Shu, Small Intestine association point (Fig. 9-11)**
Location: Lateral to the caudal border of the spinous process of the seventh lumbar vertebra, along the longitudinal line of the thoracic costal tubercula.
Innervation: Dorsal cutaneous branch of the seventh lumbar spinal nerve.
Method: Perpendicular insertion 1 to 2 cm.
Indications: Indigestion, sciatica, cauda equina syndrome.

**BL-28. Pang Guang Shu, Bladder association point (Fig. 9-11)**
Location: Lateral to the second dorsal sacral foramen, in the depression between the sacrum and the medial border of the dorsal iliac spine.
Innervation: Dorsal cutaneous branches of the first and the second spinal nerves.
Method: Perpendicular insertion 1 to 2 cm.
Indications: Urogenital disorders, cystitis, sciatica, cauda equina syndrome.

**BL-40. Wei Zhong, center of the bend (Fig. 9-12)**
He point
Location: In the center of the popliteal fossa. Under the point are the femoral artery and vein and the tibial nerve.
Innervation: Caudal cutaneous sural nerve. Method: Perpendicular insertion 0.5 to 1.5 cm deep.
Indications: Thoracolumbar disk disease, spondylitis, caudal paresis or paralysis, enuresis. Important distal point for any lumbar or hindlimb disorder.

**BL-54. Zhi bain, reaching the margin (Figs. 9-8, 9-12)**
Location: At the transection of the following two lines: the transverse line from the greater trochanter of the femur to the caudal sacrum, and the line of the sacrotuberous ligament. The point is between the two gluteal muscles, the gluteus medius and superficialis.
Innervation: Dorsal branches of the first and the second sacral nerve.
Method: Perpendicular insertion 2 to 3 cm.

**BL-60. Kun Lun, mountain (Figs. 9-8, 9-12)**
Location: In the depression between the lateral malleolus of the fibula and the attachment of the common calcaneal tendon to the calcaneal tuber.
Innervation: Caudal cutaneous sural nerve.
Method: Perpendicular insertion 0.5 cm.
Indications: Pain or paralysis of the pelvic limb, retained placenta. Local point for tarsal pain.

**BL-67. Zhi Yin, terminal Yin (Fig. 9-10)**
Jing-Well point, tonification point
Location: On the lateral coronary border of the fifth phalanx.
Innervation: Fifth abaxial dorsal digital nerve.
Method: Angular insertion proximally 0.3 cm.
Indications: Dystocia, urinary incontinence, hindlimb paresis or paralysis, ocular disorders, cardiopulmonary emergencies.

**GB-20. Feng Chi, pond of wind, wind pool (Figs. 9-6, 9-11)**
Location: In the dorsal aspect of cranial end of the head, in the shallow depression caudal to the nuchal crest of the occipital bone, at the most cranial corner of the wing of atlas, lateral to the point GV-16.
Innervation: Greater occipital nerve. This is a traditional animal point.
Method: Perpendicular insertion 0.5 to 1 cm.
Indications: Epilepsy, cervical spondylisis, cervical disk disease, Wind conditions.

**GB-34. Yang Ling Quan, spring of Yang mound (Fig. 9-8)**
He point, influential point for muscle and tendon
Location: In the depression cranial and ventral to the head of the fibula at the interosseous space. Proximal to the bifurcation of the superficial and deep peroneal nerves.
Innervation: Lateral sural cutaneous nerve. Method: Perpendicular insertion 1 to 2 cm.
Indications: Disorders of the liver, gallbladder, and pelvic limb. Muscle and tendon disorders, myopathies, knee disorders, pelvic limb paresis or paralysis. Distal point for the thoracolumbar disk disease.

**SP-6. San Yin Jiao, meeting of the Foot three Yin (Fig. 9-9)**
Location: On the medial aspect of the hindlimb, caudal to the tibia bone, three sixteenths the distance from the medial malleolus of the tibia to the stifle joint or 3 Cun proximal to the medial malleolus.
Innervation: Saphenous nerve. Deep and slightly caudal is the tibial nerve. Method: Perpendicular insertion 0.8 to 1.5 cm.

**KI-3. Tai Xi, great brook (Fig. 9-9)**
Source point
Location: In the depression caudal to the medial malleolus of the tibia and cranial to the calcanean tuberosity.
Innervation: Medial plantar branch of the tibial nerve.
Method: Angular insertion distally 0.5 cm.
Indications: Urogenital disorders: cystitis, enuresis, chronic renal disease, back pain, tarsal pain.

**GV-14. Da Zhui, large spinous process (Fig. 9-11)**
Location: On the median plane between the spinous processes of the seventh cervical and first thoracic vertebrae.
Innervation: Medial branch of the eighth cervical spinal nerve.
Method: Perpendicular insertion 2 to 4 cm.
Indications: Fever, immunodeficiency, epilepsy, cervical spondylosis, bronchial asthma. Important immune-enhancing point.

**GV-20. Bai Hui, hundreds meet (Figs. 9-1, 9-6)**

Location: On the dorsal midline of the skull, intersecting the coronal line from both sides of the rostral ear base, at the rostral end of the external sagittal crest.

- Innervation: Branches from the greater occipital, auriculotemporal, and supraorbital nerves.
- Method: Horizontal insertion caudally 0.5 to 1 cm.
- Indications: Epilepsy, anxiety, rectal or uterine prolapse.

**GV-26. Ren Zhong, center of the upper lip (Figs. 9-1, 9-6)**

Location: On the median plane of the upper lip, at the junction of its dorsal and middle third.

- Innervation: Nasal and labial branches of the infraorbital nerve.
- Method: Angular insertion dorsally 0.5 to 1 cm deep.
- Indications: Emergency, such as shock, collapse, or apoplexy, bronchitis. Important point for acute emergencies, such as shock, cardiovascular arrest and depression, collapse, coma, heatstroke, or acute epileptic attacks. Use strong stimulation (henpecking technique) in acute emergencies.

**REFERENCES**

Veterinary Acupuncture Therapy for Musculoskeletal Conditions
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Acupuncture can be a beneficial therapy for numerous musculoskeletal disorders in veterinary medicine. Appropriate medication or surgery may resolve or ameliorate many musculoskeletal conditions. It is not uncommon though to see patients for whom analgesic and antiinflammatory medications either are ineffective or are producing side effects and for whom surgical intervention either would not be beneficial or would involve risks associated with other preexisting conditions. These are times when acupuncture is indicated. Acupuncture is normally considered as a complementary therapeutic approach along with medications or surgery. In both human and veterinary acupuncture referral practices a high percentage of cases involve musculoskeletal disorders.

Kaplan states that “there is good, although limited evidence for the efficacy of acupuncture in the treatment of myofascial pain syndromes.”¹ One survey of physician acupuncturists found that myofascial pain was the second most common medical condition treated with acupuncture, and they rated acupuncture at 80–85% effective for the treatment of musculoskeletal pain.² There are numerous reports in the human medical literature on the benefits of acupuncture in musculoskeletal disorders. One study reported that 65% of clients with chronic neck and shoulder pain achieved long-term improvement after electroacupuncture.³ In 30 years of my personal veterinary acupuncture practice I have also found about an 80% success rate in the remediation of pain and improving mobility and ambulation in canine, feline and equine patients, as well as some exotic species.

Acupuncture is an excellent alternative to corticosteroid injections for tennis elbow in humans.⁴ A study of 220 human clients with chronic, low back pain from various causes showed a 79.1% success rate in satisfactory and consistent pain relief.⁵ Clients who did not have surgery before acupuncture showed a significantly higher success rate. I have observed this in my clinical practice as well.

Acupuncture was twice as effective as piroxicam, a nonsteroidal antiinflammatory agent, in the treatment of osteoarthritis.⁶ In addition, acupuncture produced no side effects, whereas piroxicam caused pruritus, intestinal bleeding, or lethargy in 19% of treated clients.⁷ In a follow-up study on clients with chronic pain, 73% were still asymptomatic after 6 years.³ In one controlled trial on 75 patients, acupuncture treatment twice weekly for 4 weeks was found to be an effective option for the treatment of patellofemoral pain syndrome in humans.⁸ This was one of the largest studies on this syndrome and acupuncture demonstrated a clear, durable effect in reducing pain and improving function.⁹ Numerous other reports have documented the beneficial effects of acupuncture for musculoskeletal conditions in humans.⁴⁻¹⁵

In the veterinary literature, there have been reports on the effects of acupuncture on degenerative joint disease, hip dysplasia, immune-mediated arthritis, and intervertebral disk disease.¹⁶⁻²¹ Janssens found in one study on 61 dogs with degenerative joint disease that response to acupuncture was better in the hip, knee and shoulder than in other joints.²¹ Chronic back pain and distal tarsal pain in horses were alleviated with acupuncture.²²,²³

Physiologic Effects
There are several theories on the physiologic effects of acupuncture in the treatment of musculoskeletal disorders. One of the primary signs of degenerative joint disease, in addition to pain and inflammation, is local stiffness caused by hypertonicity of the flexor and extensor muscles around the joint.²⁵ This is caused by an activation of the sensory A-delta and C fibers in the muscles and tendons, which is related to joint inflammation and locally released kinins. Activation of these fibers activates the gamma motor neurons of both flexors and extensors. This leads to shortened muscles with lower elasticity and thus to further joint trauma.²⁵ In addition, degenerative joint disease may lead to development of myofascial
trigger points. Some trigger points are located at the origin of permanently shortened, stiff muscles.

Acupuncture activates central endorphin-releasing systems resulting in analgesia. The “needling sensation” produced by manipulation or electrical stimulation of deep afferents from, for example, muscles and tendons may contribute to activation of the endogenous antinociceptive system. Much of the pain associated with arthritis in humans is believed to be caused by muscle spasms around joints.

One of the most effective therapeutic uses of acupuncture is for muscle pain relief. Pain relief by needling may be induced by improved circulation in the spastic muscle. Activation of a muscle vasodilator could be induced by an axon reflex caused by needling of the spastic muscle or a somatoautonomic reflex caused by needling of the distant area that corresponds to the pain-producing muscle, to improve reduced circulation.

The impulse originating from the somatic nerve endings of the needling site ascends to the contralateral anterior hypothalamus, the center of this reflex and then descends to the contralateral cholinergic vasodilatory nerve innervating the blood vessel in the pain-producing muscle. The dilated blood vessel then eliminates the pain-producing substance to relieve the pain. In addition, release of acetylcholine is facilitated by needle insertion, which produces dilatation of the blood vessel in the spastic ischemic muscle. In addition, acupuncture may act as a regulator of the alpha and gamma motor neurons. The beneficial effects of acupuncture for the treatment of musculoskeletal disorders are not associated simply with analgesia secondary to endorphin release, but are also related to increased local vasodilation and antiinflammatory effects in addition to release of trigger points and relief of stiffness and increased mobility.

The Traditional Chinese Medical (TCM) theories related to the treatment of musculoskeletal conditions are discussed in detail in “Rheumatology in Chinese Medicine.” According to TCM, osteoarthritis is analogous to Bi syndrome. The TCM description of the treatment of arthritis is beyond the scope of this paper.

**TREATMENT APPROACH TO MUSCULOSKELETAL CONDITIONS**

Before acupuncture therapy, patients should have a comprehensive examination and diagnostic workup. Radiographs, CT scans, myelograms, blood chemistry profiles, infectious tickborne disease profiles and any additional tests are performed to confirm a diagnosis. Once a diagnosis is made, all therapeutic options, including medicine and surgery, are reviewed with the client. Acupuncture may be used in conjunction with medication and surgery, postoperatively, or instead of other modalities, if appropriate. An integrative approach utilizing the best of conventional medicine and surgery, physical therapy, therapeutic lasers, ultrasound, nutritional supplements, herbal supplements and acupuncture should be considered. Acupuncture is used primarily when medication is ineffective or causing side effects and when surgery is not reasonable because of the nature of the condition or preexisting conditions that preclude surgery. Some clients prefer to try acupuncture first, before proceeding with higher-risk approaches.

Once acupuncture therapy has been selected as the treatment for the patient, the mode of stimulation and the therapeutic points must be chosen. The decision regarding which technique to use depends on the condition being treated, whether the patient requires stimulation or sedation, the type of animal being treated, and the acupuncturist’s personal preference based on experience. For instance, I sometime use traditional needle techniques, electroacupuncture, aquapuncture, or gold implants for hip dysplasia, depending on the dog’s personality and age and the severity of the condition.

The following modes of stimulation are commonly used to treat musculoskeletal conditions. I teach acupressure to my clients as an adjunct to acupuncture therapy. It can be beneficial between acupuncture treatments. I routinely will use either traditional dry needling techniques, aquapuncture,
the injection of various solutions into acupuncture points, electroacupuncture, laser acutherapy and occasionally gold implants.

There are a number of laws governing point selection. Each method has its indication and its proponents. The point selection techniques are discussed in the chapter on acupuncture point selection.

**Treatment Protocol**

Most musculoskeletal conditions treated with acupuncture are chronic, having been treated with conventional medicine or surgery before acupuncture. For a chronic problem, my initial protocol consists of acupuncture treatments 1 to 2 times a week for 3 to 5 weeks. Clients are requested to make an initial commitment to eight treatments for a dog or cat and four treatments for a horse to evaluate properly the results of acupuncture.

It is not uncommon for a patient with a chronic condition to be unresponsive until the sixth or seventh treatment, though some response is often seen within the first two to four treatments. As soon as the desired response is observed, and lasts from treatment to treatment, I taper the schedule to as few treatments as necessary to maintain the effect. That number varies a great deal. Some patients do not require further treatment, and the problem is resolved. Others require long-term management ranging from one treatment per month to one or two per year. Evaluation of response in chronic musculoskeletal conditions is based on a number of factors, similar to the ones used in evaluating the response to conventional analgesic and antiinflammatory medications and to surgery. The response is evaluated by improvement in degree of mobility of the entire animal as well as individual joints, increased activity levels, and alleviation of certain behavior patterns associated with chronic pain. These include ability to walk up and down stairs, standing up, sitting down, and desire to participate in play behavior.¹⁶

Most animals respond quite favorably to acupuncture; many relax and almost fall asleep during the treatment because of endorphin release during treatment. Few animals require sedation for treatment. Occasionally an extremely high-spirited or ill-tempered dog requires physical restraint, a muzzle, or mild sedation. This may be appropriate as long as one avoids barbiturate anesthetics; they appear to inhibit some of the effects of acupuncture. Some dogs come into the office and lie down waiting for their acupuncture. I believe that this is due to physiologic conditioning.

**Acupuncture For Specific Conditions**

**Degenerative Joint Disease**

Chronic degenerative joint disease usually responds well to acupuncture in clinical practice. One study found that 70% of dogs with chronic degenerative joint disease showed greater than 50% improvement in mobility and ambulation after acupuncture.¹⁶ The 65 dogs in this study were no longer responding to conventional medication or surgery and were recommended for euthanasia or consigned to a life of pain. Treatment of chronic degenerative joint disease with acupuncture can be very rewarding for both the veterinarian and client, in addition to the dog or cat.

The simplest technique to start with is to use traditional Chinese acupuncture needles alone in local points around the affected joints and a few distal points. Distal point selection should be based on treating the underlying TCM pattern. A dry needle technique is used, for which the needles are left in for 15 to 20 minutes. Occasionally electroacupuncture may be used on local points. Aquapuncture, moxibustion, and laser therapy may also be effective.

For degenerative joint disease in the distal foreleg, points that are beneficial include LI-4, LI-11, BL-11, BL-23, ST-36, and GB-34. In hindleg lameness, I include BL-23, BL-25, BL-40, BL-60, GB-34 and ST-36. These points are located in the atlas included in this text (Chapter 9). Local points around the affected joints include the following:
- Carpus: LI-4, TH-5, LI-6
- Elbow: LI-4, LI-10, LI-11, LU-5, HT-3
- Shoulder: LI-15, LI-16, TH-14, BL-11, LI-11
- Coxofemoral joint: GB-29, GB-30, BL-54
- Stifle: BL-21, ST-35, ST-36, SP-9, GB-30, GB-31, GB-32, GB-33, GB-34, eyes of knee (subcutaneously lateral and medial to the patellar ligament)
- Tibiotalar joint: BL-60, KI-3, LIV-3
- Vertebral column: Bladder meridian points cranial and caudal to lesions, BL-23

**Clinical Significance: Acupuncture Point Selection Rationale for Coxofemoral Degenerative Joint Disease**

Local points: GB-29, GB-30, BL-54, local trigger points
- Distal points: BL-60, BL-40, ST-36, GB-34, KI-3
- Back association points: BL-23, BL-25, BL-28
- Governing Vessel points: GV-20, GV-3, GV-4
- Points to treat underlying TCM patterns

**Clinical Significance: Acupuncture Approach for Degenerative Joint Disease in the Stifle**

Local points: ST-35, ST-36, BL-40, GB-34, eyes of the knee, SP-9, SP-10
- Distal points: BL-60, ST-45
- Additional points: BL-21, KI-3, tender and trigger points
- Mode of stimulation: electrical, manual, aquapuncture, laser
- Precautions: Do not use instead of surgery for anterior cruciate ligament ruptures if surgery is indicated.
  
  The needle insertion depth varies from point to point and from animal to animal. Techniques used and needle insertion time vary from animal to animal, based on experience.

**Vertebral Disorders**

Acupuncture is used quite successfully to treat animals with hyperpathia associated with chronic cervical, thoracolumbar, and lumbosacral disk disease. A comprehensive review of the diagnosis and treatment of disk disease has been published. Use of acupuncture for intervertebral disk disease is discussed in Chapter 14. A proper diagnosis must be made before treating conditions of the vertebral column. For example, in cases of diskospondylitis, acupuncture is beneficial as an adjunct to antibiotic therapy, but conventional medications are still required. Acupuncture is beneficial in certain cases of cauda equina syndrome. The pain usually resolves quite rapidly, and the animal returns to normal function. Each case is unique: some require periodic treatments indefinitely, whereas others resolve after four to eight treatments. Electroacupuncture with needles usually is the most effective approach in these cases. Cervical vertebral instability (wobbler syndrome) in dogs, whether from ligamentous hypertrophy, hypertrophied dorsal annulus, or disk compression, warrants a very guarded prognosis. Long-term conservative treatment is usually unrewarding, and surgery offers a guarded prognosis. Acupuncture is beneficial in about 40% of these cases. There is minimal improvement in conscious proprioception but some decrease in paresis and ataxia. If disk compression is the primary cause, the response to acupuncture is superior. If there is dorsal and ventral cord compression, the prognosis is poor.

Cervical hyperpathia secondary to cervical spondylosis, radiculopathies, or infectious organisms may respond to acupuncture. I have seen cases referred as cervical disk disease that manifested as cervical hyperpathia that were actually Lyme disease. Cervical hyperpathia is a common presentation of Lyme disease in humans and should be considered part of a differential diagnosis in animals in regions where
Lyme disease is present. Points to consider treating for cervical hyperpathia secondary to spondylosis or radiculopathies or chronic disk disease include the following:

1. Local points: BL-10, BL-11, BL-13, TH-15, TH-16, GV-14, GV-16, GB-20; local trigger points
3. Points based on underlying TCM disease patterns

   Acupuncture techniques should be chosen based on the animal’s condition.

   Thoracolumbar hyperpathia should be treated based on the cause. Hyperpathia secondary to spondylosis can be treated with local bladder meridian points, ah shi points, Hua Tuo Jia Ji points, Governing vessel points, and distal points to treat the underlying TCM pattern. Hua Tuo Jia Ji points may be quite beneficial. These points are located 0.5 to 1.0 cm lateral to the lower end of the dorsal spinous process of the vertebrae. Techniques include dry needle, moxibustion, electroacupuncture, and aquapuncture depending upon the patient’s condition.

Rheumatoid Arthritis

The treatment of rheumatoid arthritis is very complex. It involves different stages, and the key is to treat the underlying cause. Acupuncture is often used as an adjunct to conventional medical and nutritional therapy, allowing a decreased dosage of medications, thereby limiting toxicity and side effects. Treatment of root causes as discussed above for any musculoskeletal problem and symptomatic treatment is indicated.

   Symptomatic treatment should address elimination of external pathogenic factors, restoration of free circulation of Qi, and alleviation of pain.

   Point selection would include treatment of local points for affected joints and distal points for the underlying conditions. Association points for underlying deficiencies should also include BL-23 for kidney deficiency and BL-20 for deficient Blood. KI-3 and KI-6 should be considered for treating a Kidney Qi and Yin deficiency.

   Rheumatoid arthritis may also be considered a Bi syndrome. Because rheumatoid arthritis is considered an immune-mediated disorder, I use points with immunoregulatory effects. These include LI-4, LI-11, GV-14, and ST-36, in addition to local points around affected joints. In comparing the results of recent research documenting the effects of these points on immune function, it is interesting to note that the same points might be chosen according to TCM. Again, we are all speaking the same language.

Clinical Significance: Acupuncture Point Rationale for Treatment of Rheumatoid Arthritis

1. Treat local points around affected joints
2. Treat points for immune-mediated disorders (LI-4, LI-11, GV-14)
3. Treat distal points for underlying TCM disease patterns
4. Treat association points for deficiencies

Rheumatoid arthritis or chronic degenerative joint disease may also be a sequela of Lyme disease (borreliosis). Acupuncture can be a successful adjunct to appropriate antibiotic therapy in human and canine patients with Lyme disease. According to Western medicine, one would select points to support the immune system in addition to local points.

   An example is a 6-year-old, male, golden retriever brought to our hospital with a history of chronic, recurrent Lyme disease. During the 2-year illness, the dog showed left hindleg lameness and lethargy despite appropriate antibiotic and antiinflammatory therapy. The dog showed dramatic improvement in energy and attitude after the first acupuncture treatment. Lameness resolved after the third treatment. No further treatment has been required, and there has been no recurrence of Lyme disease.
Soft Tissue Conditions
Soft tissue conditions that can respond to acupuncture include myositis and other immune-mediated myofascial syndromes, tendinitis, repetitive strain injuries, and acute soft tissue trauma, such as musculotendinous sprains and strains.

Myositis
Several clinical cases of eosinophilic mandibular myositis responded well to acupuncture. I used electroacupuncture with needles on local points SI-17, SI-18, SI-19, TH-17, ST-3, and ST-6. Distal points used include GB-20, LI-4, LI-11, GV-14, and ST-36. A 4-year-old, yellow, Labrador retriever had a 4-month history of difficulty opening its mouth. Laboratory tests showed elevated eosinophil and total white blood cell counts. It responded only to corticosteroids. When corticosteroid therapy was discontinued, the dog could not open its mouth at all. Eosinophilic myositis was diagnosed by the referring veterinarian. After four acupuncture treatments, it was possible to wean the dog off corticosteroids, and the dog could open its mouth completely. After the fifth treatment, the dog was clinically normal. On 6-month follow-up, the dog was completely normal.

According to TCM, myositis may be considered an invasion of external pathogenic factors of Cold and Wind. The TCM treatment would then be to choose points to eliminate Cold and disperse the Wind. These points would include GB-20, LI-4, LI-11, GV-14, similar points as would be chosen to treat an immune-mediated disorder. Moxibustion would be considered the technique of choice. Clinically, these dogs respond quite well to moxibustion.

Clinical Significance: Soft Tissue Conditions That Can Respond to Acupuncture
- Myositis
- Tendinitis
- Repetitive stress injuries in working dogs
- Acute musculotendinous strains

Tendinitis
Acute or chronic tendinitis related to acute or repeated trauma is traditionally treated with steroidal or nonsteroidal antiinflammatory medications. Acupuncture and local trigger point therapy can be extremely effective in the specific treatment of the injury (see Chapter 15). Trigger points should be located and treated in the related muscles. Repetitive strain injuries are now being identified in working dogs, such as greyhounds, hunting, agility, and obedience trial dogs. Though no research has been conducted on the use of acupuncture for these conditions in working dogs, clinical experience by the author and other colleagues suggests acupuncture and specific trigger point therapy can be quite beneficial in resolving the problem.

Precautions and Side Effects
The most important concept to remember when considering acupuncture is that a correct diagnosis is needed before treatment. For instance, if arthritis is being treated and an undiagnosed malignancy is present, the tumor may grow faster because of increased circulation. Acupuncture should not be used if conventional medicine is more appropriate. It is important not to mask pain while the animal deteriorates and when surgery might have been more appropriate. For example, in a 1½-year-old male golden retriever with a 1-year history of right foreleg lameness, panosteitis was diagnosed by another veterinarian. Acupuncture is often beneficial in cases of panosteitis. However, no radiographs had been made. I recommended radiographs before acupuncture. Radiographically, advanced osteochondritis dissecans in the right front shoulder was diagnosed, and the dog was referred for surgery. Surgery was successful. However, 3 months postoperatively, the dog was still limping on the right front leg. Acupuncture was then recommended by the orthopedic surgeon. On reexamination, there was evidence of a knot in the triceps trigger point. After three treatments, the dog was 100% sound and has remained
that way without further treatment. Acupuncture can be quite beneficial postoperatively. However, it was fortunate that a thorough examination was performed, because surgery was certainly the initial treatment of choice.

Occasionally, an animal’s condition may deteriorate temporarily before improving. This usually lasts for only 24 to 48 hours. If an animal’s condition consistently worsens after each treatment, the diagnosis should be immediately reevaluated.

Acupuncture may be used in conjunction with nonbarbiturate analgesics and nonsteroidal antiinflammatories. It does not appear to work as well clinically in conjunction with corticosteroids. Corticosteroids tend to inhibit release of endogenous corticosteroids and endorphins, minimizing some of the beneficial effects of acupuncture. However, acupuncture will still relieve the muscle spasms. When acupuncture is used in conjunction with corticosteroids, it appears to take more treatments to observe the desired effects. I do not usually begin acupuncture simultaneously with analgesics and antiinflammatory agents because this makes it difficult to evaluate the efficacy of acupuncture. I add acupuncture subsequently only if there are insufficient results from medication or when we are trying to taper the dose of corticosteroids.

For example, a 12-year-old castrated German shepherd had severe degenerative joint disease in both coxofemoral joints and stifles. Both stifles had been operated on 3 years previously for ruptured cranial cruciate ligaments. The owner was unable to decrease the dose of corticosteroids to alternate days during more than 2 years. Early signs of iatrogenic Cushing’s disease were evident.

Acupuncture therapy was performed to treat the degenerative joint disease. After 6 treatments, corticosteroid use was reduced and then eliminated, and the patient improved considerably in attitude and ambulation. Polyuria and polydipsia decreased, and the muscles showed increased tone and strength. On a 6-month follow-up examination, the dog continued to do well without corticosteroids. Acupuncture can be used in conjunction with conventional medication and surgery, if done properly. Continuous reevaluation is important. If acupuncture is no longer helping, the condition must be reevaluated to seek other possible problems.

Many patients being treated with acupuncture are older than 10 years of age and may have multiple problems. For example, while degenerative joint disease is being treated, the animal may be developing other problems as well. When acupuncture is performed, caution must be used not to penetrate too deeply over the thorax and cause pneumothorax. Care must also be taken not to penetrate any joints. Sterility is important, and all precautions should be taken to prevent infection from lack of sterility. The advantage of acupuncture for treatment of musculoskeletal problems is that it is relatively safe and has few side effects. This cannot be said for corticosteroids and many nonsteroidal antiinflammatory agents. If surgery is not immediately essential, acupuncture can be tried first if indicated. If it does not produce satisfactory results, the surgical option is still available. The disadvantage of acupuncture for chronic degenerative joint disease is that it often requires continued treatment, which may prove difficult for some clients. Solid client commitment and good communication skills on behalf of the veterinarian are essential. Acupuncture is not a cure for arthritis but a valid treatment to help alleviate pain and improve the patient’s quality of life.

The American Veterinary Medical Association warns that the potential for abuse exists with acupuncture. The AVMA recommends that acupuncture be performed only by veterinarians with advanced training. Advanced training is definitely necessary for veterinarians who are interested in incorporating acupuncture into their practice.
**CASE STUDIES**

**Case 1**
A 9-year-old, castrated, male, collie was referred for acupuncture by an orthopedist for treatment of bilateral chronic degenerative joint disease in the carpal joints, elbow, and tarsal joints. Rheumatoid factor, antinuclear antibodies (ANA), direct and indirect Coombs', and Lyme titers were all negative. Corticosteroids caused polyuria and polydipsia. Because of the breed predisposition for rheumatoid arthritis, the animal’s nature, and the number of joints affected, I chose to treat general points for immune-mediated polyarthropathy. I treated LI-4, LI-11, ST-36, BL-40, BL-11, BL-23, GB-34, and BL-60, using traditional Chinese needles for 15 minutes. The dog showed dramatic improvement in attitude, mobility, and walking after the second treatment. By the sixth treatment, the patient showed 100% improvement. The owners claimed that the dog had not exhibited this behavior in 5 years. The dog was maintained with one treatment every 2 months and finally died at 15 years of age from unrelated causes.

**Case 2**
A 12-year-old, castrated, male, German Shepherd became nonambulatory after completion of treatment for heartworm disease. After consultation with an internist, it was concluded that lameness was caused by severe degenerative joint disease secondary to grade 4 hip dysplasia. The patient was nonresponsive to analgesics, corticosteroids, and nonsteroidal antiinflammatory agents. Because of cardiopulmonary problems secondary to heartworm disease, surgery was not recommended. Acupuncture was elected. After four acupuncture treatments the dog was ambulatory, and after six treatments the dog showed 75% improvement in mobility and ambulation. The dog continued to improve and lived to be 17 years old. He required acupuncture treatment 6 times per year after the initial series. Treatment consisted of electroacupuncture locally around each coxofemoral joint for 15 minutes. Acupuncture points used included BL-23, BL-25, BL-54, BL-40, BL-60, KI-3, GB-29, GB-30, GB-34, and ST-36. Electrical current was applied to GB-29 and GB-30.

Some of the points chosen also represent the TCM pattern of a Kidney Yin and Qi deficiency (BL-23 and KI-3).

**Case 3**
In a 6-year-old, black, Labrador Retriever with an 8-month history of severe right foreleg lameness, radiographs showed severe degenerative joint disease in the right front elbow. Medication did not resolve the lameness.

After five electroacupuncture treatments, the lameness resolved completely. At this writing, the patient is receiving preventive maintenance acupuncture 4 to 6 times per year and has shown no evidence of lameness for the past 2 years. Acupuncture points used included L-14, LI-10, LI-11 HT-3, BL-11, and the triceps trigger point. Electroacupuncture was applied across the elbow from LI-11 to HT-3 for 15 minutes per treatment.

**CONCLUSION**
Acupuncture is an excellent treatment alternative for certain musculoskeletal conditions in veterinary medicine. It is relatively safe and effective. However, it does not appear to prevent the deterioration of the overall condition or to treat arthritis systemically. Surgery should be considered when it may be more beneficial for long-term resolution of a condition. Acupuncture should be used as an adjunctive therapy in an integrative approach including nutritional supplements, botanical medicine, and conventional medications where appropriate.

As veterinary care and nutrition improve, our patients are living longer and there are more geriatric animals with chronic degenerative joint disease. As our patients age, there will be increased demand for safe, alternative therapies to maintain the quality of their lives. Acupuncture is proving to be
a beneficial therapy in the treatment of geriatric patients, especially those with degenerative joint disease.

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Acupuncture for Veterinary Neurologic Conditions
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Acupuncture has been used successfully for the treatment of various neurologic conditions in small animals. As with conventional medicine, correct diagnosis and lesion localization are essential for the best possible results. Comprehensive history, physical examination, neurologic evaluation, and any appropriate laboratory and radiographic should be conducted prior to acupuncture evaluation. The increase in the clinical use of CT scans and MRIs has increased the successful use of acupuncture for neurologic conditions as it has improved lesion localization and etiology.

Once an appropriate diagnosis is made, one can determine if acupuncture is an appropriate therapy by itself or in combination with conventional medical or surgical approaches. Acupuncture may be beneficial both preoperatively as well as postoperatively. In general, animals with traumatic, vascular, degenerative and some inflammatory nervous system disorders may benefit from acupuncture therapy. Neoplastic and infectious diseases of the nervous system are not routinely managed with acupuncture. Algorithms for the management and localization of neurologic conditions are illustrated in the “Acupuncture for Neurologic Disorders.” This chapter offers a comprehensive review of acupuncture for neurologic disorders in animals.

The primary clinical indication for acupuncture is for pain management such as in the treatment of intervertebral disc disease. Acupuncture may also be beneficial in assisting in the restoration of normal transmission of nerve impulses. It has also been found to promote healing and axonal regrowth by reducing resistance and enhancing electrical activity of injured tissues.

Acupuncture may also be beneficial when either medications are not working or are having side effects and where surgery is not feasible or when it has not worked. Response to corticosteroids may be one possible indicator as to whether acupuncture may be beneficial. For instance, in cases of degenerative myelopathy that may also be present with signs of multiple Type II disc disease, the response to corticosteroid may assist the veterinarian in deciding if acupuncture may or may not be indicated.

Once a diagnosis and lesion localization has been completed, then one can decide if acupuncture may be an appropriate treatment, either solely or as part of an integrative approach to the condition.

There are various techniques of acupuncture including dry needle technique, electroacupuncture with or without needles, aquapuncture, moxibustion, gold bead implants, acupressure and laser acupuncture. Treatment technique and duration may vary from treatment to treatment based on signs and response. Various techniques may be used to treat the same condition based on previous recommendations or the practitioner’s clinical experience. For example, I have used all these techniques at one time or another for the treatment of idiopathic esophageal achalasia. I decide on the technique based upon the individual signs that the patient is presenting at that time and based on the response to previous treatments.

The length of time of treatments, treatment frequency interval and the number of treatments also vary based on the condition of the animal, presenting signs and response to previous treatments. Typically, treatments will begin at once to twice a week, and then taper down based on response. Normal treatments may take anywhere from five to thirty minutes depending on the desired effect, sedation or stimulation of the acupoints.

One of the most common indications of acupuncture for neurologic conditions is the treatment of nonsurgical intervertebral disc disease. Acupuncture may be used in the treatment of intervertebral disc disease either alone or postoperatively, depending on the severity of the presenting signs. It has been found to be beneficial in treatment of both cervical and thoracolumbar disc disease. If acupuncture
is deemed appropriate for the particular animal, technique, point selection and duration are then selected. In general, the most common acupoint selection includes local acupuncture points along the Bladder meridian, cranial and caudal to the lesion, as well as specific distal acupoints. Distal acupoints include BL-40, BL-60, GB-34 and ST-36. Additional points along the Governing Vessel or Ting points, as well as distal points based on treating any underlying Traditional Chinese Medicine imbalances, may also be included.

Brain disorders that have been found to respond well to acupuncture include idiopathic epilepsy, cerebrovascular accidents, acute cerebral hemorrhage due to trauma, coma, as well as meningitis. Treatment of idiopathic epilepsy may decrease the frequency and severity of seizure episodes, as well as decrease the required medication doses.

Spinal cord disorders that have responded to acupuncture include fibrocartilaginous embolism (FCE), spinal cord trauma, lumbosacral disease (cauda equina syndrome) and other causes of lumbar disease. It may be used as an adjunct treatment in the treatment of discospondylitis. Degenerative myelopathy does not normally respond well to acupuncture. An integrative approach including acupuncture and nutritional supplements has been developed by Dr. Clemmons. Some cases of degenerative myelopathy that have appeared to respond to acupuncture also had concurrent multiple Type II disc disease. It has been suggested that the apparent response was due to the improvement in the disc disease component. One condition is not mutually exclusive from the other. In such cases acupuncture may be appropriate, but the prognosis is more guarded. Even though the degree of signs associated with the disc disease may improve, the progression of the degenerative myelopathy may surpass any other signs of progress.

Cervical spondylomyleopathy, commonly known as Wobbler syndrome, has had variable response to acupuncture based on the degree of spinal cord compression and whether it is both dorsal and ventral cord compression or just one or the other. Acupuncture technique will vary based on lesion localization and severity of cord compression.

Acupuncture treatment may be contraindicated for the treatment of spinal cord neoplasia. Based on clinical experience, it may possibly increase the microcirculation to the tumor site and accelerate its growth.

Peripheral neuropathies may also respond well to acupuncture. Cranial nerve VII neuropathy, trigeminal neuritis (cranial nerve V neuropathy) and geriatric peripheral vestibular syndrome (CNVIII neuropathy), as well as idiopathic peripheral vestibular syndrome and neurogenic deafness, have all responded positively to acupuncture. The success of treatment for traumatic peripheral neuropathies depends on the extent of the trauma to the nerve. Several cases of diabetic neuropathy have responded well to acupuncture. Treatment is based on both a TCM diagnosis, as well as treatment of the specific nerve.

Neuromuscular disorders and immune-mediated myopathies, such as masticatory muscle myositis (MMM) and idiopathic esophageal achalasia, have also responded well to acupuncture. Treatment is based on both a TCM diagnosis, as well as local treatment of acupoints related to specific nerves and nerve roots.

In conclusion, acupuncture may be of great benefit as a primary treatment or as an adjunct as part of an integrative approach to the treatment of neurologic conditions. The prognosis depends on the diagnosis, lesion localization severity of the condition, as well as other factors. It should definitely be considered as part of an integrative approach to neurologic conditions.
REFERENCES


Veterinary Medical Acupuncture in Critical Care Medicine
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Acupuncture (AP) may be a beneficial adjunctive therapy in numerous aspects of critical care medicine. It is not meant to be used instead of conventional medicine, but as an additional therapeutic modality or when conventional is not available. It may be used for analgesic and normoregulatory therapeutic effects based on somatovisceral reflexes. It may have beneficial effects in the treatment of cardiovascular, neurologic, gastrointestinal and urogenital emergencies. It can be used in the treatment of cardiac and respiratory depression or arrest, arrhythmias, acute pancreatitis, vomiting, diarrhea, epileptic seizures, thoracolumbar disc disease, pyometra, postoperative analgesia as well as other conditions.

Comprehensive reviews of the neurophysiologic effects and mechanism of action of veterinary AP are available.\(^1\)\(^2\) Veterinary cardiovascular conditions that may benefit from AP as an adjunct therapy include: shock and cardiac arrest, heart failure, arrhythmias and hypertension.\(^3\) AP modulates autonomic activity and thereby may correct abnormalities in blood pressure by altering heart rate, cardiac contractility and vasomotor tone. Stimulation of Large Intestine 4 (LI-4, He Gu) and Triple Heater 5 (TH-5, Wei Guan) cause vasodilation. Stimulation of Pericardium 6 (PC-6, Nei Guan) causes vasoconstriction as measured in blood flow in the toes and ears.\(^3\) One of the most commonly used points in the treatment of shock and cardiovascular collapse and arrest is Governing Vessel 26 (GV-26, Jen Chung). Needling and electrocautery of GV-26 were the most effective means of stimulation.\(^4\) GV-26 is located on the nasal philtrum at the level of the ventral aspect of the nares. Anatomical variation exists between species. Appropriate stimulation of GV-26 in dogs increases heart rate, stroke volume and cardiac output and causes pulse pressure changes that are comparable to those induced by injections of epinephrine.\(^4\)\(^5\) Stimulation also causes a significant increase in mean arterial pressure with a decrease in total peripheral resistance.\(^5\) These changes are mediated through increased sympathetic tone and may be blocked by propranolol (a nonspecific \(\beta\)-adrenergic blocker).\(^5\) Simultaneous stimulation of Kidney 1 (KI-1, Yong Quan) and GV-26 had a synergistic effect and is very useful in treating shock, anesthetic overdose and trauma.\(^4\) Large Intestine 5 (LI-5, Yang His) may correct pulsus alternans in dogs.\(^5\)

One clinical case report demonstrated the efficacy of GV-26 in reestablishing a sinus rhythm in a dog with cardiopulmonary arrest. The dog had not responded to cardiopulmonary resuscitation (CPR) with epinephrine, sodium bicarbonate and fluids. Unfortunately, in this patient the sinus rhythm could be maintained only with continued stimulation of the point.\(^6\)

When apnea was induced with thiopental in dogs, needling of GV-26 resulted in resuscitation of 88%, versus 40% when a nonacupuncture point was needled.\(^7\) AP of GV-26, KI-1 and HT-9 resulted in resuscitation of 14 of 15 zoo animals of seven different species, including ferret, serval and green monkey.\(^7\) Not all studies or all clinical experiences with the use of GV-26 for cardiovascular collapse have had positive effects.

AP needle or a small gauge hypodermic needle should be inserted perpendicularly into GV-26 and vigorously twirled while advanced and retracted without removing it from the AP point. These points, GV-26 and KI-1 may be invaluable in situations in which epinephrine is not readily available. It is certainly worth using AP stimulation either along with conventional approaches or when they have not worked or where conventional approaches are not available.

Acupuncture stimulation of Stomach 36 (ST-36, Zusanli) has been found to be of benefit in treating systemic hypertension in dogs and humans.\(^8\)
Arrhythmias frequently accompany congestive heart failure and may be associated with myocarditis and systemic disturbances. Atrial fibrillation is frequently encountered in dilative cardiomyopathy of large breed dogs. Ventricular arrhythmias may accompany boxer cardiomyopathy, traumatic myocarditis and systemic disturbances, such as gastric dilatation-volvulus and pancreatitis. AP often has a normoregulatory effect on physiologic function. Bradycardic rabbits show an increase in heart rate and tachycardic rabbits show a decrease in heart rate following stimulation of Pericardium 6 (PC-6, Neiguan). Electroacupuncture of PC-6 in rabbits increased the ventricular fibrillation threshold and had a ventricular antifibrillatory effect equal to that of lidocaine. Mild stimulation of PC-6 decreased the frequency of VPCs. AP appears to inhibit centrally mediated arrhythmias by increasing β-endorphin and dynorphin in the periaqueductal gray matter. These endorphins subsequently decrease norepinephrine and dopamine levels, reducing sympathetic stimulation of the heart.

AP for cardiovascular conditions can be quite beneficial in critical care medicine for cardiac emergencies.

AP may be beneficial for the treatment of neurological emergencies, such as acute epileptic seizures, nonresponsive status epilepticus, as well as traumatic spinal cord injury. The goal of AP in the treatment of acute epileptic seizures or status epilepticus is to break the seizure pattern and to increase the seizure threshold. The mechanism of action is currently not well understood, though the normoregulatory effect of acupuncture on electroencephalographic activity is believed to be the main effect.

AP is not meant to be a substitute for conventional antiepileptic medications, but is used when they are not working or in emergencies where they are not available. AP points to consider for the treatment of status epilepticus include GV-20, GV-26, KI-1, HT-7, PC-6 and an emergency point at the tip of the ear. Dry needle stimulation is suggested.

Traumatic spinal cord injuries may benefit from AP. AP has been found to improve function in rats and decrease atrophy of the spinal cord white matter, in addition to sparing the ventral horn motor neurons if used within 1 hour after trauma. AP in spinal trauma has been shown to modulate electrolyte and free-radical generation and serum cortisol, β-endorphin, serotonin, LDH and SGPT levels. Local AP points, cranial and caudal to the lesion, along the bladder meridian and distal extremity points related to the affected spinal cord segments, are suggested.

AP can be extremely beneficial as an adjunctive therapy in the treatment of GI motility disorders, such as acute vomiting and diarrhea. AP has a normoregulatory effect on GI motility through somatovisceral reflexes. It can also be beneficial for its analgesic and antiinflammatory effects in the treatment of acute pancreatitis. Numerous studies document the efficacy of AP for GI conditions. AP points that are documented as efficacious in acute GI disturbances include Pericardium 6 (PC-6, Neiguan) and Stomach 36 (ST-36, Zusanli) as well as segmental paraspinal bladder meridian points, such as Bladder 20, 21, 25.

A unique urogenital effect of AP is in the stimulation of uterine motility in an open pyometra. AP points associated with uterine motility, including BL-28 and SP-6, may be beneficial in stimulating the expulsion of purulent vaginal discharge. AP points to stimulate the immune system, LI-4, LI-11, ST-36 and GV-14 may be beneficial in increasing the response to infection.

In recapitulation, AP may be extremely beneficial as an adjunctive therapy in the treatment of many critical care patients including cardiovascular, neurological, gastrointestinal, urogenital and other conditions.

References


The following papers are compiled to accompany the presentations scheduled in the continuing education sessions at the convention. The proceedings are organized by day and by stream as follows:

**SATURDAY, JULY 13**

- Companion Animal - Endocrinology
- Companion Animal - Emergency Medicine
- Companion Animal - Exotic Animals
- Equine - Equine Parasite Control
- Equine - Equine Field Anesthesia
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- Integration of Mind/Body Medicine (MBM) into Veterinary Practice and Daily Life
**Canine Hypoadrenocorticism: Diagnosing and Treating the Difficult Cases**

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**INTRODUCTION**

Hypoadrenocorticism (Addison’s disease) results from failure of the adrenal glands to secrete glucocorticoids and mineralocorticoids. Most cases of hypoadrenocorticism are due to primary adrenal failure, resulting in deficiency of usually both cortisol and aldosterone from the adrenal cortex. More rarely, Addison’s disease may be due to pituitary dysfunction resulting in a failure of ACTH secretion and pure glucocorticoid deficiency (secondary adrenal failure). In secondary hypoadrenocorticism, mineralocorticoid secretion is expected to be normal.

**CLINICAL SIGNS**

**Signalment**

Seventy percent of dogs diagnosed with hypoadrenocorticism are female, and most are young to middle-aged dogs (mean 4–5 years). The disease is heritable in the Standard Poodle, Bearded Collie, Portuguese Water Dog, and the Nova Scotia Duck Tolling Retriever (NSDTR), and in these breeds no obvious sex predisposition is evident. In the Standard Poodle, Portuguese Water Dog, and NSDTR, the disease appears to be inherited as an autosomal recessive trait. Incidence of hypoadrenocorticism in the NSDTR is estimated to affect 1.4% of the population, while in the Standard Poodle 8.6% of poodles in one study were affected.

**History and Physical Examination**

Clinical signs may be either acute or gradual in onset and often wax and wane. Owners may not realize how long their dog has been ill until treatment results in a dramatic improvement in activity level. Since 85–90% of adrenal reserve must be depleted before clinical signs are observed, it may require a stressful event to trigger clinical illness. Clinical signs may be very vague. Anorexia, vomiting, lethargy/depression, weakness, weight loss, diarrhea, shaking/shivering, polyuria, polydipsia, and abdominal pain may be observed. Most of these clinical signs can occur due to glucocorticoid deficiency alone. If mineralocorticoids are also deficient, the clinical signs tend to be more severe, and polyuria, polydipsia, hypovolemic shock, collapse, and dehydration are often present. Less common clinical signs include acute gastrointestinal hemorrhage and seizures due to hypoglycemia or electrolyte derangement. The physical examination may be normal or may reveal lethargy, weakness, dehydration, bradycardia, weak pulses, decreased capillary refill time, and other evidence of hypovolemic shock.

**DIAGNOSTIC TESTING FOR HYPOADRENOCORTICISM**

**Clinical Pathology**

A complete blood count may reveal a nonregenerative normocytic normochromic anemia; alternatively the hematocrit may be increased due to dehydration. Eosinophilia, neutrophilia or lymphocytosis are found in only 20–30% of dogs with hypoadrenocorticism, but lack of a stress leukogram in a dog with systemic illness is common. A chemistry profile may reveal hyponatremia, hypochloremia, hyperkalemia, hypercalcemia, and hyperphosphatemia. These changes occur due to aldosterone deficiency with a resultant failure of the kidneys to conserve sodium. Other possible serum biochemical abnormalities include hypoalbuminemia, hypcholesterolemia, hypoglycemia, and increased liver enzymes. Specific gravity of the urine is commonly less than 1.030. The changes on the minimum database in dogs with
hypoadrenocorticism may initially mimic other disorders such as renal failure, hepatic disease, gastrointestinal disease, or insulinoma.

**Serum Electrolyte Abnormalities**
The majority of dogs with hypoadrenocorticism have the classic electrolyte changes of hyponatremia and hyperkalemia due to aldosterone deficiency.

**Na:K Ratio**
The Na:K ratio is usually low in dogs with hypoadrenocorticism, and this ratio may be useful to guide emergency diagnosis and treatment while waiting for definitive test results.

**Imaging Studies**
Most untreated dogs with hypoadrenocorticism have one or more radiographic abnormalities on thoracic and abdominal radiographs, including microcardia, small cranial lobar pulmonary artery, narrow posterior vena cava, or microhepatica. Occasionally dogs may have evidence of megaesophagus. Most dogs with hypoadrenocorticism have a measurable reduction in size of the adrenal glands, and sometimes the adrenal glands cannot be identified on ultrasound.

**Electrocardiogram**
In dogs with hyperkalemia, abnormalities may be present on the electrocardiogram. These include a peaked T wave and shortening of the QT interval in mild hyperkalemia, widening of the QRS complex, decreased QRS amplitude, increased duration of the P wave, and increased P-R interval in moderate hyperkalemia, and loss of P waves and ventricular fibrillation or asystole in severe hyperkalemia.

**Basal Cortisol**
Measurement of a basal cortisol of > 55 nmol/l (2 microg/dl) is a useful test to exclude a diagnosis of hypoadrenocorticism. Measurement of a basal cortisol concentration is not adequate for confirmation of a diagnosis of hypoadrenocorticism, however, because some dogs have a low basal cortisol concentration but have an appropriate response to ACTH administration.

**ACTH Stimulation Test**
An ACTH stimulation test is necessary to confirm a diagnosis of hypoadrenocorticism, because not all dogs with hypoadrenocorticism have the expected electrolyte changes, and because many other disorders may mimic the characteristic findings of Addison’s disease. In dogs with hypoadrenocorticism, both the pre- and post-ACTH cortisol concentrations are usually less than 27 nmol/l (1 microg/dl), and both values should be less than the reference range for basal cortisol (usually 55 nmol/l, 2 microg/dl) to confirm the diagnosis.

**ATYPICAL ADDISON’S DISEASE**
It is now recognized that although most dogs with hypoadrenocorticism have obvious electrolyte changes such as hyponatremia and hyperkalemia, a subset of dogs with hypoadrenocorticism lack these electrolyte changes. In a retrospective study of dogs with hypoadrenocorticism, 24% of dogs lacked hyponatremia and hyperkalemia. In a study of 25 NSDTR, 32% lacked electrolyte abnormalities at the time of diagnosis. Reasons for normal electrolytes include secondary hypoadrenocorticism due to decreased ACTH secretion, selective destruction of the zona fasciculata and reticularis, early-stage disease in which there has not yet been complete destruction of the zona glomerulosa, or ability to compensate for sodium wasting by increasing sodium intake. Dogs with glucocorticoid-deficient hypoadrenocorticism tend to be older, have a longer duration of clinical signs, and are more likely to be anemic, hypoalbuminemic, and hypocholesterolemic than those with electrolyte changes.
**How Does Recognition of Atypical Addison’s Disease Change the Diagnostic Approach?**

It is important for clinicians to recognize that an absence of the characteristic electrolyte changes of hyponatremia and hyperkalemia does not exclude a diagnosis of hypoadrenocorticism. Clinicians should have a high index of suspicion for hypoadrenocorticism so that this very treatable disease is not missed. Conversely, reliance on measurement of electrolytes alone for diagnosis of hypoadrenocorticism can be misleading, because there are many other causes of hypernatremia and hyperkalemia; the diagnosis must be confirmed by endocrine testing.

When evaluating any systemically ill dog, the possibility of hypoadrenocorticism should always be considered. Useful clues may be the presence of waxing and waning illness, improvement with conservative management, and improvement after administration of glucocorticoids. Lack of a stress leukogram and the identification of small adrenal glands on ultrasound also increase suspicion for hypoadrenocorticism. In dogs with suspected hypoadrenocorticism, measurement of a basal cortisol is useful to exclude the diagnosis without the expense of an ACTH stimulation test.

**Acute Treatment**

Rapid treatment of dogs with suspected Addison’s disease is vital, especially if profound electrolyte abnormalities are present. Aims of treatment include correction of hypotension/hypovolemia, correction of electrolyte imbalances, provision of an immediate source of glucocorticoids, and correction of acidosis, hypoglycemia, and hypercalcemia.

The suggested procedure for dogs presenting with signs of hypovolemia in which Addison’s disease is suspected is detailed below:

Place IV catheter in cephalic or jugular vein and collect a blood sample for measurement of electrolytes and cortisol. Synthetic ACTH (5 microg/kg) is then administered IV, and a second blood sample for measurement of cortisol collected 1 hour later. Fluid therapy (0.9% saline IV, 30–80 ml/kg/24 hours plus correction for dehydration) should be started immediately. Once the second blood sample has been collected, treatment with glucocorticoids can begin if there is a high clinical suspicion of Addison’s disease. If the animal is in shock, administration of steroids should be at shock doses, and this should take precedence over establishing an immediate diagnosis. The choice of mineralocorticoid depends upon the clinical status of patient (oral versus injectable), product availability, and confidence in diagnosis. In most cases, electrolytes normalize with fluid therapy and glucocorticoids alone, and immediate mineralocorticoid supplementation is not necessary. Long-term mineralocorticoid therapy can be initiated once the animal is stable and the diagnosis is confirmed. Other treatments that may be indicated in individual patients include synthetic colloids, blood transfusion, and IV dextrose. Parameters that should be monitored during treatment include serum electrolytes and acid-base status, urine output, ECG, blood pressure, and, if possible, central venous pressure. IV fluid therapy should be continued until the animal is fully rehydrated and oral intake is possible.

**Maintenance Therapy**

Options for long-term mineralocorticoid treatment include fludrocortisone (starting dose 0.02 mg/kg/day as a single dose or divided) or desoxycorticosterone pivalate (starting dose 2.2 mg/kg q 25 days). For both of these mineralocorticoids, the dose should be titrated to effect. The dose of fludrocortisone typically needs to be increased over time, whereas in many cases the final individualized dose of DOCP is < 2.2 mg/kg.

Prednisone is typically recommended for glucocorticoid replacement. The starting dose is 0.2 mg/kg per day, and the dose should then be tapered to the lowest dose that will control the clinical signs. It is important to avoid excess prednisone supplementation, because this may result in manifestations of iatrogenic hyperadrenocorticism. Only 50% of dogs treated with fludrocortisone
require supplemental prednisone, whereas most dogs treated with DOCP require prednisone at least every other day.

**How Does Diagnosis of Atypical Addison’s Disease Change the Diagnostic Approach?**

The main difference between managing dogs with classic Addison’s and those with atypical Addison’s disease is that dogs without electrolyte derangements do not require mineralocorticoid treatment and respond well to treatment with glucocorticoids alone. Treatment costs are therefore much cheaper. Doses of prednisone required to control the clinical signs are typically < 0.1 mg/kg/day, and some dogs can be managed on every-other-day treatment. If significantly higher doses of prednisone are required to control the clinical signs, the possibility of an alternative diagnosis should be considered.

Dogs with atypical Addison’s should be monitored using clinical signs reported by the owner, physical examination findings (especially weight), and measurement of electrolytes. Serum electrolyte concentrations should initially be monitored frequently, because some dogs that present without electrolyte derangements will develop them later. The ACTH stimulation test is not part of the regular monitoring for animals with either classic or atypical Addison’s disease.

**References**

Diagnosis of Canine Hyperadrenocorticism: What is the Role of Sex Hormone Profiles?
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INTRODUCTION
Approximately 80 to 85% of cases of spontaneous canine hyperadrenocorticism (HAC) are due to pituitary-dependent hyperadrenocorticism (PDH), with the remainder due to an adrenocortical tumor (AT). Cortisol is the most common secretory product of the adrenal gland in HAC, although excessive secretion of other adrenal hormones has also been documented.

SIGNALMENT
The median age for HAC in dogs is 11 years. There is a slight increased predisposition for females (55–65%). Larger breeds may be affected more frequently with AT than smaller breeds.

CLINICAL SIGNS OF HYPERADRENOCORTICISM
Common clinical signs include polydipsia, polyuria, polyphagia, abdominal enlargement, hepatomegaly, cutaneous changes, muscle weakness, decreased exercise tolerance, excessive panting, and hypertension. Less common clinical signs include lethargy, insulin-resistant diabetes mellitus, incontinence, while rarely thromboembolism, ligament rupture, and pseudomyotonia are recognized. Neurologic abnormalities observed in pituitary macrotumor syndrome include behavior changes, inappetence, stupor, aimless wandering, circling, pacing, and ataxia.

LABORATORY CHANGES IN HYPERADRENOCORTICISM
Common laboratory abnormalities include neutrophilic leukocytosis, eosinopenia, lymphopenia, thrombocytosis and polycythemia. Changes on the biochemistry panel include increased alkaline phosphatase (ALP), milder increases in alanine aminotransferase (ALT) activity, hypercholesterolemia, hyperglycemia, and hypertriglyceridemia. Urinalysis may reveal low urine specific gravity, glucosuria, proteinuria or evidence of urinary tract infection. Urinalysis may show indications of a urinary tract infection, proteinuria, and a low urine specific gravity. Dogs with HAC also have increased risk for calcium oxalate urolithiasis.

DIAGNOSIS OF HYPERADRENOCORTICISM
Diagnosis of Cushing’s syndrome is made by consideration of historical findings, physical examination, review of a laboratory minimum database (CBC, serum biochemical profile, urinalysis), and performance of specific endocrine function tests. Common clinical tests for HAC include the ACTH stimulation test, low-dose dexamethasone suppression (LDDS) test, and urine cortisol:creatinine ratio. Measurement of a baseline cortisol has no value for diagnosis. Testing for HAC should be performed in dogs with consistent clinical signs of HAC, clinical signs of a pituitary macrotumor, dogs with poorly controlled diabetes mellitus and suspected insulin resistance, dogs with an adrenal mass, and dogs with persistent hypertension. Testing should not be initiated based on laboratory abnormalities alone. It is important to remember that systemic illness can interfere with testing and result in false-positive test results; testing for HAC should be postponed until the patient is clinically well.

WHICH TEST SHOULD BE PERFORMED FIRST?
The cortisol:creatinine ratio is an excellent screening test for spontaneous HAC. If clinical signs of HAC are present and there is no history of exogenous corticosteroid administration, the LDDS is the most
appropriate confirmatory test. If this test is abnormal or borderline, the ACTH stimulation test may be used to confirm or support the diagnosis and obtain a baseline for monitoring response to treatment. If HAC is not confirmed by the LDDS test, an ACTH stimulation test may be performed if clinical suspicion for the disease is high. Testing should be repeated in 1–3 months if testing is negative but no other cause of the clinical signs is identified. In dogs with obvious clinical signs of HAC and persistent normal cortisol testing, measurement of a sex hormone profile may be considered (see below). In animals with suspected iatrogenic HAC, the ACTH stimulation test is the test of choice.

**Urine Cortisol:Creatinine Ratio**
The UCCR provides an integrated reflection of cortisol production, thereby adjusting for fluctuations in blood cortisol concentrations. The reported sensitivity of the UCCR ranges from 75%–100% when the sample is randomly collected in the hospital, while the reported specificity is 20–25% in dogs with clinical signs of HAC. If two samples are collected at home at least 2 days after a veterinary visit, the UCCR performs better; predictive value of two basal UCCRs above the cut-off level is 0.88 and that of a negative test result is 0.98. Because of concerns about the specificity of the UCCR, a positive result should be confirmed by a second test. A UCCR well within the reference range makes a diagnosis of HAC unlikely. Reference ranges for UCCR vary between laboratories.

**Low-Dose Dexamethasone Suppression Test**
The LDDS demonstrates decreased sensitivity to glucocorticoid feedback in dogs with HAC. The LDDS relies on the fact that the administration of exogenous glucocorticoids should suppress the production of ACTH from the normal pituitary and therefore the production of cortisol from the normal adrenal. This suppression persists in normal dogs for 16–24 hours. Since dexamethasone is not detected by the cortisol assay, cortisol suppression can be measured after administration of exogenous dexamethasone. In dogs with pituitary-dependent HAC, the pituitary gland is less sensitive to glucocorticoid feedback while adrenal tumors function independently of ACTH, and, in addition, dexamethasone is metabolized more quickly in dogs with HAC. For these reasons, in dogs with either form of HAC, no suppression occurs 8 hours after low-dose dexamethasone administration. The LDDS test has a sensitivity of 85–100% and a specificity of 44–73%. The LDDS should not be used before iatrogenic HAC has been excluded. The LDDS test requires a blood sample for the measurement of a baseline cortisol, followed by the administration of dexamethasone (dexamethasone sodium phosphate or dexamethasone in polyethylene glycol) IV at a dose of 0.01 mg/kg. The patient is then left undisturbed in a cage, and a second blood sample is collected 8 hours later. In normal dogs, the second sample will show suppression of the cortisol concentration typically to less than 1.0 µg/ml. Dogs with HAC do not demonstrate this suppression. Additional information may be obtained by measuring a cortisol concentration 4 hours after dexamethasone administration. If suppression occurs at 4 hours but “escape” occurs at 8 hours, this is diagnostic for PDH and further differentiation testing is unnecessary.

**ACTH Stimulation Test**
The ACTH stimulation test relies on the assumption that hyperplastic or neoplastic adrenals have abnormally large reserves of cortisol and therefore hyperrespond to maximal stimulation by ACTH. Dogs with iatrogenic HAC will have a suppressed response to ACTH. The recommended protocol is collection of a baseline sample, administration of synthetic ACTH (Cortrosyn, cosyntropin, tetracosactin) at a dose of 5 µg/kg IV. A second sample is collected one hour later. In order to interpret the ACTH stimulation test, reference ranges must be established for each laboratory. The sensitivity of the ACTH stimulation test ranges between 57–83%, while specificity is between 86–93%. Sensitivity is only 57–63% in dogs with functional adrenal tumors. The ACTH stimulation test does not distinguish between ADH and PDH but is useful in distinguishing between iatrogenic and spontaneous HAC. Because of the low sensitivity of this test, the ACTH stimulation test is not the first test of choice for spontaneous HAC. The ACTH
stimulation test can be performed at any time of day, and use of compounded ACTH is discouraged. Cosyntropin/Cortrosyn can be reconstituted and frozen (e.g., in aliquots) at -20°C in plastic syringes for 6 months; whether Synacthen can be frozen has not been investigated.

**Differentiation of PDH From Adrenal Tumors**

Endocrine function tests such as the high- and low-dose dexamethasone suppression tests, endogenous ACTH concentration and diagnostic imaging are used to differentiate PDH from AT. Suppression of a basal cortisol concentration by more than 50% 4 or 8 hours after administration of either a low or high dose of dexamethasone is diagnostic for PDH. Lack of suppression, however, is not diagnostic for ADH and additional testing is required. If greater than 50% suppression is seen at 4 or 8 hours on a LDDS, a HDDS test is unnecessary. Measurement of canine ACTH concentration is also useful in differentiating PDH from AT. In dogs with AT, ACTH concentration should be low, whereas in dogs with PDH the concentration is normal or high. Reference ranges for endogenous ACTH vary between laboratories and assays. Because of episodic secretion of ACTH in PDH, the ACTH concentration ranges from low to high, and the ACTH concentration should never be used alone to confirm a diagnosis of adrenal tumor.

**Diagnostic Imaging**

Approximately 57% of adrenal tumors are identified on abdominal radiographs as a soft-tissue mass or a mineralized opacity, compared to 72% with ultrasonography. Other radiographic findings may include hepatomegaly, osteopenia, dystrophic mineralization and distension of the urinary bladder. Thoracic radiographs may reveal evidence of metastasis, pulmonary thromboembolism or mineralization. In dogs with PDH, ultrasound of the adrenal glands typically reveals bilaterally symmetrical enlargement of the adrenal glands with preservation of normal adrenal architecture. The glands may not be identical in size, but the smaller adrenal gland in dogs with PDH typically has a dorsoventral width greater than 5 mm. The size of the adrenal glands may be within the normal range in some dogs with PDH. In dogs with a functional adrenal tumor, there is unilateral adrenal gland enlargement with abnormal adrenal gland architecture, while the contralateral adrenal gland is small (< 5 mm in dorsoventral width). Evidence of tumor thrombus within the vena cava is detected on ultrasound in 11% of dogs with adrenocortical tumors, and evidence of distant metastasis to the liver, kidneys, and other abdominal organs may be present. Bilateral adrenal tumors and macronodular hyperplasia of the adrenal gland in dogs with PDH may complicate the interpretation of ultrasound findings. Computed tomography is also a useful tool for evaluating the adrenal glands, especially in dogs with adrenal tumors. MRI or CT of the brain is helpful in determining pituitary tumor size in dogs with PDH. Approximately 70% of dogs with PDH have a detectable pituitary tumor on CT or MRI.

**Atypical or Occult Hyperadrenocorticism**

These terms are used to describe dogs in which clinical signs and response to treatment are consistent with a diagnosis of HAC, but the standard screening tests (ACTH stimulation test, low-dose dexamethasone suppression test) results are within the reference range. The reasons for the clinical signs in these patients are currently unknown. It has been proposed that increased circulating concentrations of steroid adrenal hormones other than cortisol (e.g., progesterone, 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone) may be responsible for the clinical signs in occult HAC, but this is controversial except in the few documented cases of sex hormone-secreting adrenal tumors. Sex hormone-secreting adrenocortical tumors can be identified because of the presence of an adrenal mass; in these dogs, cortisol concentration after ACTH administration is typically suppressed below the reference range. Although dogs with apparent pituitary-dependent occult HAC have been reported in the literature, they are rare. Other potential reasons for normal screening test results in occult HAC patients may include individuals with increased sensitivity to
glucocorticoids, inappropriately high reference ranges for cortisol in dogs with early or mild HAC, as well as rare forms of HAC such as food-dependent HAC.

**SEX HORMONE PROFILES IN DOGS WITH HYPERADRENOCORTICISM**

Hormones that have been reported to be increased in the few documented cases of occult HAC include serum dehydroepiandrosterone, androstenedione, progesterone, and 17-hydroxyprogesterone. Concentration of 17-hydroxyprogesterone and progesterone in dogs with HAC has been evaluated more extensively than other sex hormones. Studies suggest that sensitivity and specificity of progesterone for diagnosis of HAC are 88% and 55%, and for 17-hydroxprogesterone are 91% and 59%, respectively. Sex hormone testing should not be considered as first-line testing for dogs with HAC. Measurement of sex hormone profiles should only be considered in dogs with clinical signs of HAC that have repeated normal LDDS and ACTH stimulation test results and no other cause for their clinical signs identified. One indication for testing that is well accepted is the presence of inappropriately low cortisol concentrations on HAC screening tests in dogs with no exposure to exogenous glucocorticoids (suggestive of sex hormone-secreting AT).

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Treatment of Canine Hyperadrenocorticism: Mitotane or Trilostane?
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In the United States, most dogs with canine pituitary-dependent hyperadrenocorticism (PDH) are treated medically with either opDDD (mitotane) or trilostane. Hypophysectomy, the treatment of choice for PDH in people, is not commonly performed in dogs in the US, although it is more commonly performed in Europe. Although surgery is often considered the treatment of choice for adrenal tumors, medical therapy with mitotane and trilostane can also be effective. It is ideal to identify which form of hyperadrenocorticism is present when formulating an approach to treatment. Tests that may be used to differentiate PDH from AT include the low- and/or high-dose dexamethasone suppression tests, measurement of endogenous ACTH concentration, and imaging studies such as ultrasound and computed tomography. If identification of the cause of hyperadrenocorticism is not possible, mitotane is a good choice for treatment when the underlying cause of the problem is unknown.

Both mitotane and trilostane may be effective in management of both pituitary-dependent and adrenal-dependent forms of hyperadrenocorticism, and both drugs have advantages and disadvantages. In some cases it may be necessary to transition a patient from trilostane to mitotane or vice versa. Reasons for changing from one drug to the other include adverse drug effects, disease relapse, owner’s preference or ability to monitor the patient, and medication costs. When planning the drug transition, it is important to understand the different mechanisms by which these drugs control the clinical signs of hyperadrenocorticism and the different protocols for administration of the drugs.

Mitotane
Mitotane is derived from the insecticide DDT and is a potent adrenocorticolytic agent. The drug causes progressive necrosis of the zona fasciculata and zona reticularis of the adrenal gland and at higher doses may also cause necrosis of the zona glomerulosa. Other effects of mitotane include fatty degeneration, centrilobular atrophy and congestion of the liver. Normal dogs are clinically quite resistant to the effects of the drug. Mitotane should never be administered in animals that are not eating well. Therapy with mitotane is begun at a dose of 50 mg/kg divided q 12 hours. Glucocorticoids are not usually administered concurrently, but a small supply of prednisone should be made available to the owner for emergencies. Mitotane at induction doses is typically administered for 5–10 days, until water consumption decreases to < 100 ml/kg/day. It should be discontinued immediately if a decreased appetite, depression, diarrhea, or vomiting are observed. At this point the dog should be reevaluated and an ACTH stimulation test performed. Prednisone treatment (0.1 to 0.2 mg/kg) should be initiated in patients that are showing clinical signs of hypocortisolemia, until the results of the ACTH stimulation test are known. In patients that are not polydipsic, patients in which water consumption cannot be monitored, and patients in which polydipsia is due to another underlying disease (e.g., diabetes mellitus), mitotane should be administered for a maximum of 5–7 days prior to ACTH stimulation testing. The goal of treatment is to have both the pre- and post-cortisol measurement in the normal resting range (2–6 microg/dl). Maintenance therapy (50 mg/kg q 7–10 days) is started once the ACTH stimulation test shows adequate suppression and prednisone therapy (if necessary) has been discontinued. Failure to use maintenance therapy will result in regrowth of the adrenal cortex and recurrence of clinical signs. Efficacy of maintenance therapy is monitored by an ACTH stimulation test in 1 month and thereafter every 3–4 months. The dose of mitotane required for long-term maintenance is very variable (26–330 mg/kg/week). Reasons for treatment failure include incorrect diagnosis, the presence of an adrenal tumor (although some adrenal tumors will respond well), loss of drug potency due to poor storage or compounding of mitotane, or a need for a higher dose or duration of treatment.
in some dogs. Side effects of mitotane include gastric irritation, hypoadrenocorticism, and very occasionally neurologic signs. Mean survival time of 200 dogs treated with mitotane was 2.2 years (range 10 days to 8.2 years).

TRILOSTANE

Trilostane is a synthetic hormonally inactive steroid analogue, which is a competitive inhibitor of the 3 β-hydroxysteroid dehydrogenase system. The drug blocks synthesis of adrenal steroids including cortisol and aldosterone. Trilostane is rapidly absorbed orally (peak concentrations within 1.5 hours), although suppression of plasma cortisol concentrations is short lived (< 20 hours). Current recommendations for use of trilostane are to start at a dose of 1–6 mg/kg q 12–24 hrs and then increase or decrease the dose based on evaluation of ACTH stimulation tests performed 4–6 hours after drug administration. Twice-a-day therapy at a starting dose of 1–3 mg/kg may result in good control of clinical signs at a lower total daily dose with less risk of adverse effects than higher doses q 24 hours. ACTH stimulation testing should be performed 10, 30, and 90 days after start of treatment and 30 days after each dose adjustment. Trilostane is well tolerated in most dogs. Adverse effects that are usually mild and self-limiting include diarrhea, vomiting, and lethargy in up to 63% of treated dogs. Occasionally dogs have developed hypoadrenocorticism, which is generally glucocorticoid deficient only, although dogs with evidence of mineralocorticoid deficiency have been reported. Hypoadrenocorticism induced by trilostane is generally reversible, although in rare cases this may take several months - likely because of adrenocortical necrosis. There have been anecdotal reports of acute death shortly after starting trilostane treatment. In a recent retrospective study of dogs treated with either mitotane (n = 25) or trilostane (n = 123), long-term survival was not statistically different between the groups. Median survival in the mitotane group was 708 days (range 33–1399), and in the trilostane group was 662 days (range 8–1971). Of the dogs that died in this study, 11% died due to causes that were attributed to the underlying PDH, and a further 17% died of causes that could have been related to their underlying PDH. In 38% of cases, the cause of death could not be directly attributed to PDH, and in 34% the cause of death was unknown.

Other drugs that have been reported to be useful for treatment of dogs with PDH include ketoconazole, cabergoline, retinoic acid and l-deprenyl. Radiation therapy improves outcome in dogs with PDH that have associated neurological signs due to a pituitary tumor and in dogs with pituitary tumors greater than 0.8 to 1.0 cm in diameter.

TREATMENT OF ADRENOCORTICAL TUMORS

Treatment of adrenal neoplasia involves either surgical resection of the tumor or medical therapy with mitotane, trilostane or ketoconazole. Adrenalectomy should be reserved for patients that do not have evidence of extensive tumor invasion or metastasis. Abdominal ultrasound and computed tomography can assist in planning the surgical approach. The surgical approach may be made via a midline or a paracostal approach. A midline approach allows visualization of both adrenals and other abdominal organs; however, the paracostal approach allows better exposure of the affected adrenal gland. After unilateral adrenalectomy, normal adrenal gland tissue will be atrophic, and glucocorticoid and sometimes mineralocorticoid supplementation is necessary in the perioperative and postoperative period. Dexamethasone provides primarily glucocorticoid replacement. This should be administered in IV fluids over 6 hours as soon as the tumor is identified. Alternatively, hydrocortisone can be used as a continuous infusion to provide both glucocorticoid and mineralocorticoid supplementation. Other options for mineralocorticoid support include fludrocortisone or desoxycorticosterone pivalate administered 12–24 hours before surgery. Blood pressure, central venous pressure, electrolytes and blood glucose should be carefully monitored before, during and after surgery. The merits of preoperative anticoagulant administration to prevent thromboembolic complications have yet to be
proven. After surgery, parenteral glucocorticoids should be continued for 48–72 hours until the patient is bright, alert and eating. Oral supplementation with prednisone can then replace parenteral therapy. Supplementation with mineralocorticoids, if utilized, should be discontinued after 2 doses and the patient monitored for the development of hyperkalemia or hyponatremia. The prognosis for those with adrenocortical tumors without metastatic disease that survive the initial perioperative period is good. In one study, 80% of dogs survived the perioperative period.

Some dogs with inoperable tumors or metastatic disease may respond to medical treatment with high doses of op-DDD (mitotane). Mitotane is often successful in controlling clinical signs and in some cases may also result in tumor shrinkage. In one study, the mean dose of mitotane required to control clinical signs in dogs with adrenal tumors ranged from 35 to 1275 mg/kg/week. Ketoconazole and/or trilostane may also be used for palliation of clinical signs or to improve clinical signs prior to adrenalectomy. If in one study, there was no difference in survival times for dogs with adrenal tumors treated with either mitotane or trilostane.

**TRANSITIONING FROM MITOTANE TO TRILOSTANE**

The most common reasons to transition from mitotane to trilostane include adverse effects of mitotane and frequent relapse of clinical signs while on mitotane treatment. Important data to obtain prior to the transition include a complete history and physical examination, review of endocrine testing, and diagnosis of cause of hyperadrenocorticism (pituitary-dependent versus functional adrenal tumor). Mitotane should be discontinued prior to starting trilostane therapy. It is recommended to wait at least one month after discontinuation of mitotane before starting trilostane. Trilostane should not be initiated until there is recurrence of clinical signs of hyperadrenocorticism, and until the post-ACTH cortisol concentration is within the upper reference range or greater than the upper limit of the reference range. Close monitoring of adrenal function is advised, as dogs previously treated with mitotane seem to be more responsive to the effects of trilostane. Trilostane treatment should be initiated at the lower end of the dose and ACTH stimulation testing performed as recommended above.

**TRANSITIONING FROM TRILOSTANE TO MITOTANE**

The most common reasons to transition from trilostane to mitotane include adverse effects of trilostane (e.g., hyperkalemia) and treatment of dogs with adrenal tumors. The adrenal glands become enlarged in dogs treated with trilostane, and trilostane has no inherent cytotoxicity for adrenal tumors. Mitotane, on the other hand, can result in shrinkage of adrenal tumors. Although this would suggest that mitotane is the preferable drug to use in dogs with functional adrenal tumors, survival studies of dogs with adrenal tumors have shown similar survival with both drugs. Important data to obtain prior to the transition include a complete history and physical examination, review of endocrine testing, and diagnosis of cause of hyperadrenocorticism (pituitary-dependent versus functional adrenal tumor). Trilostane should be discontinued prior to starting mitotane therapy. Mitotane should not be initiated until there is recurrence of clinical signs of hyperadrenocorticism and until the post-ACTH cortisol concentration is within the upper reference range or greater than the upper limit of the reference range. Because of the short half-life of trilostane, a long washout period between the two drugs is usually not necessary; however, close monitoring of adrenal function is advised, as dogs previously treated with trilostane may be more sensitive to the effects of mitotane because of the adrenal hyperplasia induced by trilostane. Mitotane should be initiated at the standard induction dose and the dog monitored carefully for signs of hypoadrenocorticism as described above. An ACTH stimulation test should be performed after induction and then after the first 30 days of maintenance therapy.
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What’s New in Feline Hyperthyroidism?
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INTRODUCTION
Hyperthyroidism is a syndrome caused by the excessive production and secretion of the thyroid hormones T3 and T4 by an autonomous thyroid gland. Feline hyperthyroidism was first reported in 1979, and since then it has become a common disease in cats. Histopathology of affected thyroids usually reveals thyroid hyperplasia or benign thyroid adenoma; however, in a small percentage of cases thyroid adenocarcinoma is diagnosed. Pathologic changes may affect one or both lobes of the thyroid gland. In addition, ectopic thyroid tissue may be present within the neck or thorax. Ectopic tissue may sometimes be difficult to distinguish clinically from metastasis of thyroid adenocarcinoma. Feline hyperthyroidism is the most common endocrine disease of cats older than 8 years (mean age 12.8± 0.2 years). Most studies have shown no sex or breed predisposition, although Siamese and Himalayan cats are underrepresented, and in one study female cats were found to be at increased risk.

APPROACH TO DIAGNOSIS AND TREATMENT OF FELINE HYPERTHYROIDISM
The minimum database necessary for evaluation of a cat with hyperthyroidism includes a detailed history and physical examination, serum thyroxine (T4) concentration, complete blood count, serum chemistry panel, urinalysis, thoracic radiographs, and arterial blood pressure. Other diagnostic tests that may be indicated in some patients include cardiac ultrasound, abdominal radiographs, ophthalmologic examination, and an ECG. A technetium scan is strongly recommended in all hyperthyroid cats prior to surgical thyroidectomy.

Because hyperthyroidism is a disorder of geriatric cats, it is important to actively investigate for the presence of concurrent disease and to take into account the special needs of geriatric patients when planning therapy. Identification of concurrent illness may prompt further diagnostic investigation, influence prognosis, and often influences choice of therapy.

History/Physical Examination
Clinical signs that are suggestive of hyperthyroidism include weight loss, diarrhea, vomiting, polyphagia, polyuria, polydipsia, muscle weakness, poor hair coat, and hyperactivity. Anorexia and lethargy are also seen in a smaller subset of patients. Findings on physical examination in addition to the clinical signs noted above may include tachycardia, heart murmur, signs of cardiac failure, cardiac arrhythmias, dehydration, and a palpable thyroid nodule. Ventroflexion of the neck is seen in a small percentage of patients. A combination of the above findings is highly suggestive of hyperthyroidism; however, other disorders common in older cats such as renal failure, congestive heart failure, gastrointestinal disease, and diabetes mellitus may mimic some or all of this constellation of the clinical signs.

Laboratory and Radiographic Findings
The complete blood count is usually normal, although polycythemia (47% cases) or a stress leukogram may be present. A biochemical chemical panel usually reveals mild to moderate increases in ALT (SGPT) and alkaline phosphatase. Other common findings include azotemia and hypokalemia. Hyperglycemia (stress induced) and azotemia (concurrent renal disease or prerenal azotemia) are also common findings in hyperthyroid cats. Thoracic radiographs may reveal cardiomegaly (due to hypertrophic cardiomyopathy), pleural effusion, pulmonary edema, or pericardial effusion. Thoracic radiographs may also identify evidence of concurrent diseases such as primary or metastatic neoplasia. Hyperthyroid cats with cardiomegaly alone usually do not require additional treatment other than control of the hyperthyroid state; however, cats that have evidence of congestive heart failure need specific therapy.
for hypertrophic cardiomyopathy. Echocardiography is indicated in hyperthyroid cats with evidence of more severe cardiac disease as demonstrated by significant cardiomegaly, pulmonary edema, pleural effusion, or cardiac arrhythmias. Echocardiography will often show evidence of mild hypertrophic cardiomyopathy in cats with no other signs of heart failure; however, in this circumstance the only treatment that is usually required is control of the hyperthyroid state. Most cardiac changes resolve after treatment of the underlying disorder; however, some severe cardiomyopathies do not resolve after treatment and require continued therapy. Occasionally, dilated cardiomyopathy occurs in cats with hyperthyroidism. An electrocardiographic evaluation is important if cardiac arrhythmias are detected on physical examination. The most common abnormalities are sinus tachycardia and increased amplitude of the R wave (lead II). Hypertension is identified in 15–20% of hyperthyroid cats at the time of diagnosis of hyperthyroidism. Approximately 20% of hyperthyroid cats develop clinically significant hypertension months (median 5 months) after treatment of hyperthyroidism. It is therefore important that blood pressure be monitored carefully before and after treatment of hyperthyroidism.

**DIAGNOSIS**

A diagnosis of hyperthyroidism can usually be confirmed by measurement of a single serum T4 concentration. In some cats with early hyperthyroidism and those with concurrent nonthyroidal disease, the T4 concentration may intermittently fluctuate into the normal range.

If the T4 is high normal or borderline, diagnostic options include repeating the measurement of serum T4 at a later date after concurrent diseases have been treated and/or the hyperthyroid state has become more severe, or measurement of a free T4 concentration (by equilibrium dialysis or equivalent assay). Other diagnostic options include a T3 suppression test, TRH stimulation test, or a technetium scan. A study of 917 hyperthyroid cats, 221 cats with nonthyroidal illness, and 172 clinically normal cats evaluated the usefulness of measurement of free T4 (measured by direct equilibrium dialysis) as a diagnostic test for hyperthyroidism. The sensitivity of the free T4 concentration (98.5%) as a diagnostic test for hyperthyroidism was significantly higher than the sensitivity of the T4 concentration (91.3%); however, the specificity was lower with 14 of the sick euthyroid cats having false-positive results by free T4. The free T4 concentration is a sensitive test for use in cats with suspected hyperthyroidism with a normal T4 concentration; however, the test should only be used in conjunction with the total T4 concentration. Some cats with a low T4 concentration and a high free T4 concentration are euthyroid. In this situation (low to low-normal T4 and high free T4), other factors - such as presence of a palpable thyroid mass, clinical signs, and presence of concurrent nonthyroidal illness - need to be taken into account, and further diagnostic testing such as a T3 suppression test or technetium scan should be considered.

In cats in which the total T4 and free T4 are normal but hyperthyroidism is still suspected, a T3 suppression test should be considered. To perform a T3 suppression test, baseline T3 and T4 concentrations are measured and then T3 is administered at a dose of 25 µg/cat orally q 8 hours for 7 treatments. Second T3 and T4 concentrations are then measured 4–6 hours after the last treatment. In euthyroid cats, a suppression of greater than 50% of baseline or less than 2 µg/dl for the post-T4 value should occur. Failure to suppress is consistent with a diagnosis of hyperthyroidism. T3 concentrations are measured pre- and post-T3 administration to confirm client compliance and adequate absorption of the drug.

In most cats, if the T4 concentration is in the low or low-normal range, a diagnosis of hyperthyroidism is unlikely and other diagnoses should be pursued; however, recent studies suggest that some hyperthyroid cats with concurrent illness can have very low T4 concentrations. Whether a diagnosis of hyperthyroidism should be pursued in an individual cat with a low or low-normal T4 depends upon the clinical signs and physical examination. A technetium scan may be the most useful diagnostic test in these cats. Spontaneous acquired hypothyroidism is extremely rare in the cat, so in
most cases the finding of a low T₄ concentration should prompt investigation for nonthyroidal disease rather than further evaluation of the thyroid axis.

It is not uncommon to palpate a cervical nodule in a cat with no clinical or laboratory signs of hyperthyroidism. Possible differential diagnoses include early hyperthyroidism in which a goiter is present but the thyroid gland is not fully autonomous, thyroid cyst, or nonfunctional thyroid adenoma or carcinoma. Nonfunctional thyroid carcinoma does occur but is rare in the cat. If an obvious cervical nodule is palpated in a cat with a normal T₄ concentration, a fine-needle aspirate should be considered to determine the tissue of origin. Unfortunately, the accuracy of cytology for differentiation of benign from malignant thyroid disease is poor.

**TREATMENT**

A number of options are available for the treatment of feline hyperthyroidism. These include antithyroid drugs (oral or transdermal), surgical thyroidectomy, radioactive iodine therapy, and nutritional management with an iodine-limited diet. The choice of treatment depends on the presence and severity of concurrent nonthyroidal illness, the age of the cat, the cat’s tolerance for hospitalization, adverse effects of antithyroid medications, owner preference, and the results of other diagnostic tests (cardiac evaluation, technetium scan).

**Antithyroid Drugs**

Oral antithyroid drugs are indicated in most hyperthyroid cats prior to definitive therapy and in some cases may be the treatment of choice for long-term therapy. Antithyroid drugs are especially useful in extremely old patients, in patients with serious concurrent medical problems, as test therapy in patients with renal failure, and in cases where the cost of definitive therapy is not possible for the owner. The antithyroid drug of choice is methimazole, which should be initiated at a starting dose of 2.5–5 mg q 8–12 hours and then titrated to effect. Most cats (90%) become euthyroid within 2–3 weeks of starting therapy. The dose required to maintain euthyroidism is quite variable from cat to cat (2.5–20 mg/day). A small percentage of hyperthyroid cats may be resistant to the effects of methimazole. Adverse clinical reactions occur in up to 20% of cases and include anorexia, vomition, lethargy, excoriation of the head and neck, icterus, and bleeding diatheses. Mild hematological abnormalities develop in 16% of cats and include leucopenia, lymphocytosis, and eosinophilia. More severe hematologic abnormalities develop in 4% of cats and include agranulocytosis and thrombocytopenia. Cats on antithyroid drugs should have a CBC, platelet count, and T₄ concentration performed every 2 weeks for the first 3 months of therapy. A recent study of 44 hyperthyroid cats compared response to treatment with oral methimazole compared with topical methimazole for treatment of hyperthyroidism. Cats were treated with methimazole at a dose of 2.5 mg q 12 hours. Seventeen cats received oral methimazole, whereas 27 cats received methimazole in a Pluronic lecithin organogel (concentration 5 mg/0.1 ml), which was applied to the non-haired portion of the pinna. After 4 weeks of treatment, 9/11 cats treated with oral methimazole were euthyroid, compared with 14/21 cats treated with topical methimazole. This difference was not statistically significant. Cats treated with oral methimazole had a higher incidence of gastrointestinal side effects (4/17 cats) than those treated topically (1/27), but there was no difference in the incidence of other side effects.

Propylthiouracil (PTU) is also an effective antithyroid drug in cats, but the risk of adverse reactions is significantly higher. For this reason it is no longer recommended in cats. The advantages of oral antithyroid drug therapy include the low cost, avoidance of anesthesia, and avoidance of a surgical procedure. The disadvantages include the risk of side effects, failure to respond in some patients, problems with owner compliance, and control rather than cure of disease. Survival in cats treated with methimazole alone is significantly shorter than that of cats treated with radioactive iodine. Long-term antithyroid drug therapy is best used in cats with severe concurrent nonthyroidal illness, in very old
patients, and in those cases where the owner cannot afford definitive treatment. Methimazole is often used in patients with renal failure to evaluate the effect of euthyroidism on renal function. If BUN and creatinine remain stable or increase only slightly after euthyroidism is achieved, it is likely definitive therapy will be well tolerated. If there is a significant increase in BUN or clinical signs of renal failure after treatment, consideration should be given to titration of the methimazole dose with the aim of controlling clinical signs of hyperthyroidism with the smallest possible dose of methimazole. Definitive therapy with $^{131}$iodine or thyroidectomy should be avoided in these cats.

**Thyroidectomy**

The advantages of surgical thyroidectomy include rapid response to treatment, short hospital stay, convenience in the private practice setting, and opportunity to evaluate surgically excised thyroid tissue histopathologically. Disadvantages include the need for general anesthesia, the risk of inducing iatrogenic hypoparathyroidism, morbidity associated with the surgical procedure, and the higher cost when compared to antithyroid medication. Whether cats treated with surgery have a higher risk of recurrent disease than those treated with $^{131}$iodine has not been proven. If surgical thyroidectomy is the treatment chosen, careful attention should be paid to the presurgical cardiac evaluation, choice of anesthetic protocol, and fluid therapy. If there is evidence of significant cardiac disease, medical therapy should be used to stabilize the patient prior to surgery. Methimazole together with atenolol or diltiazem is usually effective in controlling the hyperthyroid state and improving cardiac function. In some cases, diuretic therapy may also be necessary. Surgery is most appropriate in those patients in which there is unilateral thyroid involvement based on the results of a technetium scan. In cases of bilateral thyroid disease, the owners need to fully understand the potential risk of hypoparathyroidism. In all cases of bilateral thyroidectomy, cats should be carefully monitored for signs of hypocalcemia for 3–5 days after surgery, because it is difficult to predict at the time of surgery whether or not clinical hypocalcemia will occur. If it is not possible to perform a technetium scan prior to surgery, the whole cervical region should be explored at the time of surgery. Ectopic thyroid tissue is found in as many as 12% of hyperthyroid cats. Normal thyroid tissue should be atrophic, so thyroid tissue that appears grossly active is abnormal. Rate of recurrence after surgical thyroidectomy is 5–12%.

**Radioactive Iodine**

The thyroid gland concentrates iodine within the colloid of the gland. Radioactive iodine emits $\beta$ particles that destroy functional thyroid tissue without causing damage to normal tissues, such as the parathyroid glands. Normal thyroid tissue is spared because it is atrophic due to lack of TSH, and it does not concentrate much iodine. $^{131}$iodine is the radionuclide of choice for the treatment of hyperthyroidism. It has a half-life of 8 days and is a beta and gamma emitter. The beta particles travel a maximum of 2 mm in tissue, so they cause only local destruction within the thyroid gland. The advantages of radioactive iodine therapy are that it is safe; anesthesia is not required; and it is effective for the treatment of ectopic thyroid tissue or metastatic thyroid carcinoma. The disadvantages are the expense; limited availability; lack of opportunity to evaluate thyroid tissue histopathologically; and requirement for isolation in an approved facility from several days to 2 weeks following treatment, depending on local regulations. Antithyroid drugs should be discontinued 7–14 days prior to treatment. $^{131}$iodine is administered IV or SC at a dose that is either a fixed dose (4–6 millicuries) or a calculated dose based on the weight of the cat, the size of the thyroid gland, and the $T_4$ concentration. In animals known to have thyroid carcinoma, doses of 20–30 millicuries are used. $T_3$ and $T_4$ concentrations decline in 5–10 days, and clinical improvement is usually observed within 2 weeks of treatment, although in some cats the response may be delayed. Hypothyroidism may occur in cats secondary to bilateral thyroidectomy or radioactive iodine therapy. In many cases, this is transient and unassociated with clinical signs. Persistent hypothyroidism decreases glomerular filtration rate and has been associated
with decreased survival in azotemic cats. Clinical signs of hypothyroidism in cats include anorexia, lethargy, weight gain, poor hair coat, and alopecia.

The advantages of $^{131}$I-iodine therapy are that all sites of thyroid tissue are destroyed; there is no risk of hypoparathyroidism; no anesthesia is required; and it is possible that the risk of recurrence may be lower. Radioactive iodine therapy should be avoided in patients with severe concurrent nonthyroidal illness, especially those that require therapy during isolation; in cats with renal failure that worsens with the use of antithyroid drugs; and in those patients that do not tolerate hospitalization well.

**Nutritional Management**

Dietary iodine restriction to less than 0.32 ppm reduces the circulating thyroid hormone concentrations into the normal range in hyperthyroid cats. Dietary iodine restriction has potential as an alternative management strategy for feline hyperthyroidism, because thyroid hormone synthesis requires iodine. There is now a commercially available iodine-limited diet marketed for management of feline hyperthyroidism (Hill’s y/d). The diet is similar in formulation to Hill’s g/d but has an iodine content ≤ 0.3 ppm and is available as both a canned and dry food. Ninety percent of hyperthyroid cats will become euthyroid when fed a limited-iodine diet exclusively. The most common reason for failure to control the hyperthyroidism is access to iodine-containing food such as treats, human food, or other pet foods. Even small amounts of other iodine-containing foods can result in an increase in the TT₄ concentration. An iodine-limited diet should not be combined with oral antithyroid drugs because of the risk of profound hypothyroidism. Nutritional management is an alternative option for management of hyperthyroidism in cats that are not good candidates for definitive treatment of their hyperthyroidism because of concurrent nonthyroidal illness, adverse effects from antithyroid drugs, or owner finances. Although cats managed with an iodine-limited diet become euthyroid, a thyroid adenoma is still present. Information about long-term outcome for cats with feline hyperthyroidism managed by iodine restriction has not yet been published. Nutritional management is not a good option for cats that go outside and can access other sources of dietary iodine, and for those cats that need to be on a controlled diet to manage concurrent nonthyroidal illnesses that require dietary therapy, such as inflammatory bowel disease, allergic dermatitis, or heart disease. In cats with early renal failure and concurrent hyperthyroidism, Hill’s y/d may be an acceptable diet, because it is supplemented with omega-3 fatty acids, contains controlled amounts of phosphorus sodium, and has high-quality protein (36% dry-matter basis). Cats in more severe renal failure may need to be on a more restricted protein diet. Hyperthyroid cats in multi-cat households need to be fed individually, and access to food of other pets in the household must be prevented. Alternatively, the iodine-limited diet can be fed to all cats in the household, provided the euthyroid cats are supplemented daily with a small amount of food with higher iodine content. In cats that do not become euthyroid within 4–8 weeks of starting a limited-iodine diet, a detailed history should be investigated for evidence of other sources of iodine. Possible sources of iodine in addition to access to other pet foods include well water, use of medications or supplements, contaminated food bowls, and access to human food.

**References**


Insulin Therapy in Canine and Feline Diabetes Mellitus: An Update
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PATHOPHYSIOLOGY OF DM
Diabetes mellitus (DM) is a common endocrine disease in dogs and cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition, the lack of insulin results in increased gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism. Factors that have been identified as predisposing factors in cats include obesity, advancing age, and being male. In dogs, older females are at higher risk of developing DM. Poodles, Dachshunds, Miniature Pinschers, Beagles, Golden Retrievers, and Miniature Schnauzers are considered to be at higher risk than the general canine population. Keeshonden appear to have a genetic predisposition to the disease.

Two types of DM are recognized in man, and these classifications can be applied to the disease in dogs and cats. Type I DM (insulin-dependent diabetes mellitus) is due to an absolute deficiency of insulin. This form of diabetes is characterized by minimal secretory response to β-cell secretagogues such as glucagon, and it is the most common form of diabetes recognized in the dog. Type II DM (noninsulin-dependent diabetes) is characterized by abnormal insulin secretion and peripheral insulin resistance, and it results in a stable deregulation of the blood glucose concentration at a higher concentration. This type of DM is rare in the dog but is common in the diabetic cat. The two types of diabetes are classically distinguished by characteristic responses to challenge by insulin secretagogues such as glucose, glucagon, or arginine. In type I DM, there is a decreased or negligible secretion of insulin compared to normal animals, whereas in Type II DM, total insulin secretion may be normal or increased, although the pattern of secretion may be abnormal. The insulin concentration is still insufficient, however, to prevent hyperglycemia. The phenomenon of glucose toxicity complicates interpretation of glucagon tolerance tests, particularly in cats, and the glucagon tolerance test is of little practical utility in clinical practice.

DIAGNOSIS
The diagnosis of DM is made based on characteristic clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss) and documentation of hyperglycemia and glycosuria. In dogs, the diagnosis is usually straightforward; however, in cats it may be complicated by the occurrence of marked stress hyperglycemia. When making a diagnosis of DM in cats, it is therefore important not only to document persistent hyperglycemia and glycosuria, but also to rule out other diseases that may cause similar clinical signs. Measurement of fructosamine concentrations or urine glucose of samples collected in the home environment may allow the clinician to distinguish between stress-induced hyperglycemia (and resultant glycosuria) and persistent hyperglycemia due to diabetes mellitus. Glucosuria may also occur secondary to ketamine anesthesia, chronic renal failure, and postobstructive diuresis, so it is not on its own diagnostic for diabetes mellitus. The presence of significant ketonuria together with hyperglycemia is diagnostic for diabetes mellitus in both dogs and cats.

Cats are also unique in that DM in this species may be transient or intermittent. In clinical studies, 15 to 70% of cats with DM have been reported to go into spontaneous clinical remission, with achievement of good glycemic control. Unfortunately, the glucagon tolerance test is not useful in predicting whether or not a cat is likely to go into remission. In dogs, diabetes mellitus is usually permanent, unless DM occurs secondary to profound insulin resistance due to hormones such as progestogens and glucocorticoids. This type of diabetes is sometimes referred to as type III DM. In these
cases, if the diagnosis is made early and the cause of insulin resistance can be removed, the diabetes may also resolve.

**INSULIN THERAPY**

**Classification of Insulin**

It is very important for clinicians prescribing insulin to understand their classification. Insulin may be classified by insulin source, insulin formulation, or duration of action. Not all forms of insulin are currently commercially available, and product availability is likely to continue to change. Insulin formulations that have been available historically include short-duration regular insulin (designated R), moderate-duration NPH insulin (designated N), moderate-duration Lente insulin (designated L), long-duration Ultralente insulin (designated U), and long-duration PZI insulin. Insulin may be derived from bovine, porcine, or human recombinant sources, and the concentration may be either 100 units/ml (human products) or 40 units/ml (veterinary products). A number of human recombinant insulin analogues are also available.

The types of insulin recommended for use in dogs and cats have been complicated by the recent disappearance of many insulin products from the market. The insulin products that are currently available in the US are listed below.

**Insulin products currently available and recommended for use in dogs and cats:**

- **Short-acting:**
  - Regular insulin (Zinc insulin crystals)
    - Products: Humulin R (Lilly), Novolin R (NovoNordisk) - Both human recombinant. 100 U/ml
  - Moderate-acting:
    - NPH insulin (neutral protamine hagedorn)
      - Complexed with protamine zinc in phosphate buffer
      - Products: Humulin N (Lilly), Novolin N (NovoNordisk) - Both human recombinant. 100 U/ml
    - Lente insulin
      - Mixture of 30% semilente and 70% ultralente insulin
      - Products: Caninsulin/Vetsulin (MSD Animal Health) Pork insulin, 40 U/ml (currently not available)
  - Long-acting:
    - PZI insulin
      - Insulin complexed with protamine and zinc
      - Products: ProZinc (Boehringer Ingelheim) - human recombinant (40 U/ml)
    - Glargine
      - Insulin analogue
      - Products: Lantus (Sanofi-Aventis) - human recombinant (100 U/ml)
    - Detemir
      - Insulin analogue
      - Products: Levemir (NovoNordisk) - human recombinant (100 U/ml)

**Insulin Therapy in Cats**

Insulin products that are most suitable for use in cats include PZI and glargine insulin. The starting dose for insulin in a new feline diabetic patient is 0.25–0.5 Unit/kg or 1–3 U/cat. It is recommended that insulin be started at the lower end of this dose.
It is difficult to predict in advance which cats will do better with which insulin formulation. Cats should be carefully monitored for occurrence of hypoglycemia because of the possibility of remission of diabetes mellitus in the cat. A blood glucose curve (5–14 days) should be performed after making any change in insulin formulation. Twice-a-day insulin therapy is more likely to result in good glycemic control than once-a-day therapy. If twice-a-day treatment is not possible, once-a-day therapy with PZI or glargine can result in effective control of clinical signs in some cats.

**Insulin Therapy in Dogs**

The most effective insulin formulation in dogs that is currently available is human recombinant NPH (Humulin N) at a starting dose of 0.5 U/kg twice a day. Lente insulin is also an effective insulin for use in dogs but is currently not available. Use of human recombinant insulin or pure pork insulin avoids the complications that can occur due to development of antiinsulin antibodies in dogs treated with beef/pork insulin. Long-acting insulins, such as PZI, glargine, and detemir are unpredictable in dogs and are not appropriate for the management of most diabetic dogs; however, treatment with these products may be necessary in dogs that have a very short duration of action when treated with NPH insulin. Detemir has been evaluated in a small number of diabetic dogs. It is important to be aware that this insulin is much more potent in the dog than other insulin, with the dose needed for good glycemic control ranging from 0.07–0.23 U/kg.

**Monitoring the Diabetic Patient**

Assessment of the regulation of diabetic control in diabetic dogs and cats should involve evaluation of clinical signs. Other tools include measurement of blood glucose concentrations, urine glucose concentrations, and measurement of glycated proteins (fructosamine). Monitoring should be individualized to meet the needs of the patient and owner.

**Starting dose and dose range for insulin products used in diabetic dogs**

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Starting dose</th>
<th>Median dose</th>
<th>Dose range</th>
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<tbody>
<tr>
<td>NPH</td>
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<td>0.5 U/kg</td>
<td>0.2–1.0 U/kg</td>
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<tr>
<td>Lente</td>
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<td>PZI</td>
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<td>Glargine</td>
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<td>0.1–1.1 U/kg</td>
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<tr>
<td>Detemir</td>
<td>0.1–0.2 U/kg</td>
<td>0.07–0.23 U/kg</td>
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**Goals of Insulin Treatment**

The primary goal of insulin therapy in diabetic patients is to control clinical signs of DM while avoiding hypoglycemia. Severe hypoglycemia can be life-threatening, and even mild insulin-induced hypoglycemia can result in clinical signs of poor glycemic control due to the insulin resistance that results from secretion of antiinsulin hormones such as glucagon, growth hormone, cortisol, and epinephrine. Persistent, severe hypoglycemia can lead to neuronal loss. The benefits of tight glycemic control, while well established in human diabetic patients, have not been demonstrated in dogs and cats that have a shorter lifespan; although, theoretically, better glycemic control should result in fewer diabetic complications such as recurrent infection, proteinuria, and cataract formation. The goals of diabetic regulation should therefore take into account the lifestyle of the owner, the presence of concurrent illness, the age of the patient, and the practicality of tight glucose monitoring.

Ideally, the blood glucose should be maintained between 100 and 200 mg/dl; however, most patients will have some blood glucose concentrations that fall outside this range, and most patients are clinically well regulated if most of the blood glucose concentrations are less than 300 mg/dl. The pre-insulin blood glucose concentration is typically the highest blood glucose measurement in dogs. Occult
hypoglycemia is an important cause of poor glycemic control and can lead to unnecessary visits to the emergency clinic. The insulin dose should be decreased if the blood glucose falls below 80 mg/dl on the BG curve. It is important to remember that it is difficult to assess the duration of insulin action if the glucose nadir is in the hypoglycemic range, because this can lead to release of counter-regulatory hormones such as glucagon, which drives the blood glucose back up prematurely.

**Diabetic Remission**

A unique feature of diabetes mellitus in cats is that some diabetic cats become noninsulin dependent after treatment has been initiated. Approximately 15 to 70% of cats with DM have been reported to go into spontaneous clinical remission after initiation of insulin treatment. This is termed diabetic remission. Diabetic remission is typically defined as normoglycemia that persists for greater than 4 weeks without the use of exogenous insulin. The duration of remission is variable with some cats requiring insulin treatment again within a few weeks to months and other cats remaining in remission for months to years. If diabetic remission occurs in cats, it is most commonly in the first few months of treatment. Low-carbohydrate diets in conjunction with good glycemic control increase the likelihood of diabetic remission.

Other factors that have been documented to increase the likelihood of diabetic remission in cats include short duration of diabetes mellitus (<180 days), administration of glucocorticoids prior to diagnosis, low insulin dose required to achieve glycemic control, and lack of polyneuropathy. Age, sex, body weight, presence of renal failure, presence of hyperthyroidism, or presence of obesity at diagnosis have not been shown to influence the likelihood of remission.

**Switching From One Insulin Product to Another**

1. Evaluate how well regulated the animal is on current insulin product.
2. Determine potency of new insulin versus old insulin (long-acting insulins are less potent than moderate-acting insulins).
3. Determine frequency of new insulin administration.
4. Determine new dose based on these factors: If animal has good glycemic regulation or if you are switching to a more potent insulin or increasing the frequency of administration, decrease dose by 15–20%; if animal is not tightly regulated and potency of insulin is the same or less, keep the same dose. Larger dose adjustments may be needed with changes in frequency of insulin administration.
5. Educate owners about obtaining and using U40 insulin syringes if you are switching to U40 insulin. The same applies when switching from U100 to U40 insulin. Educate owners about the clinical signs of hypo- and hyperglycemia. Make sure they know how to treat an episode of hypoglycemia.
6. Evaluate response to new insulin by evaluating clinical signs and by performing a blood glucose curve 5–7 days after making the product change. The dose should be increased or decreased in appropriate increments for the size of the dog or cat.

**Dietary Management**

Dietary management should be instituted at the same time as insulin therapy in the diabetic patient. The goal of dietary therapy is to minimize postprandial fluctuations in blood glucose and to potentiate the action of insulin.

Studies support the feeding of a high complex-carbohydrate (>50% dry matter), high-fiber diet (>10% dry matter) to dogs with DM. Diets containing increased amounts of soluble fiber (fruits, legumes, oats) delay gastric emptying, alter intestinal transit time, and potentiate the actions of insulin in tissues. Increased amounts of insoluble fiber (cellulose, vegetables, grains) alter intestinal transit time and slow starch hydrolysis. The net effect of a high-fiber diet is to slow glucose absorption from the intestinal tract, reduce postprandial fluctuations in blood glucose, and enhance glycemic control of the diabetic
Reduced fat diets are probably appropriate in diabetic patients due to their susceptibility to hepatic lipidosis, pancreatitis, and hypercholesterolemia. Research suggests that high-fiber diets may also improve glycemic control in cats; however, other clinical data suggests that feeding a low-carbohydrate diet is preferable in diabetic cats (carnivore connection theory) and may improve glycemic control. A prospective study comparing a low-carbohydrate, low-fiber diet to a moderate-carbohydrate/high-fiber diet in 63 diabetic cats showed improvements in glycemic control in both groups, but there was a higher rate of remission of diabetes mellitus in the low-carbohydrate/low-fiber diet. These findings support the clinical opinion that low-carbohydrate diets in conjunction with good glycemic control increase the likelihood of diabetic remission. If diabetic remission occurs in cats, it is most commonly in the first few months of treatment.

Currently I recommend starting with a low-carbohydrate diet in newly diagnosed diabetic cats and switching to a high-fiber diet if there is a poor response to the low-carbohydrate diet, particularly if there are problems with weight gain on the low-carbohydrate diet.

The daily caloric intake should be designed to correct obesity and maintain ideal body weight. Obesity has been shown to cause reversible insulin resistance in man due to its effects on insulin receptors. This also appears to be important in cats in which reversal of obesity may improve or reestablish normal glycemic control. In dogs, reversal of obesity may improve glycemic control and decrease the requirement for insulin, but it is unlikely to replace the need for insulin therapy. The feeding schedule is also very important in diabetic patients. Feeding should occur when insulin is present in the bloodstream in order to utilize glucose as it is absorbed. Multiple feedings are preferable since this will help minimize the hyperglycemic effect of each individual meal. Ideally, 3–4 small meals/day should be fed; however, the schedule of most owners limits the ideal feeding schedule. For those dogs receiving insulin twice a day, at least four meals would be ideal. In most cases, however, two meals are fed at the same time as insulin is administered. As in every aspect of management of the diabetic patient, a regular and consistent feeding schedule is the most important factor. The same principles apply to the dietary management of diabetic cats. In obese cats or those in multi-cat households, the ration should be meal fed to ensure a consistent and if necessary a calorie-restricted diet. For others, allowing cats to nibble a dry ration throughout the day seems to work well.

References


Management of Difficult Diabetes Cases: A Case-Based Approach
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PATHOPHYSIOLOGY OF DM
Diabetes mellitus (DM) is a common endocrine disease in dogs and cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition, the lack of insulin results in increased gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism. Factors that have been identified as predisposing factors in cats include obesity, advancing age, and being male. In dogs, older females are at higher risk of developing DM. Poodles, Dachshunds, Miniature Pinschers, Beagles, Golden Retrievers, and Miniature Schnauzers are considered to be at higher risk than the general canine population. Keeshonden appear to have a genetic predisposition to the disease.

Two types of DM are recognized in man, and these classifications can be applied to the disease in dogs and cats. Type I DM (insulin-dependent diabetes mellitus) is due to an absolute deficiency of insulin. This form of diabetes is characterized by minimal secretory response to β-cell secretagogues such as glucagon, and it is the most common form of diabetes recognized in the dog. Type II DM (noninsulin-dependent diabetes) is characterized by abnormal insulin secretion and peripheral insulin resistance, and results in a stable reeregulation of the blood glucose concentration at a higher concentration. This type of DM is rare in the dog but is common in the diabetic cat. The two types of diabetes are classically distinguished by characteristic responses to challenge by insulin secretagogues such as glucose, glucagon, or arginine. In type I DM, there is a decreased or negligible secretion of insulin compared to normal animals, whereas in Type II DM, total insulin secretion may be normal or increased, although the pattern of secretion may be abnormal. The insulin concentration is still insufficient, however, to prevent hyperglycemia. The phenomenon of glucose toxicity complicates interpretation of glucagon tolerance tests, particularly in cats, and the glucagon tolerance test is of little practical utility in clinical practice.

DIAGNOSIS
The diagnosis of DM is made based on characteristic clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss) and documentation of hyperglycemia and glucosuria. In dogs, the diagnosis is usually straightforward; however, in cats it may be complicated by the occurrence of marked stress hyperglycemia. When making a diagnosis of DM in cats, it is therefore important not only to document persistent hyperglycemia and glucosuria, but also to rule out other diseases that may cause similar clinical signs. Measurement of fructosamine concentrations or urine glucose of samples collected in the home environment may allow the clinician to distinguish between stress-induced hyperglycemia (and resultant glucosuria) and persistent hyperglycemia due to diabetes mellitus. Glucosuria may also occur secondary to ketamine anesthesia, chronic renal failure, and postobstructive diuresis so is not on its own diagnostic for diabetes mellitus. The presence of significant ketonuria together with hyperglycemia is diagnostic for diabetes mellitus in both dogs and cats.

Cats are also unique in that DM in this species may be transient or intermittent. 15 to 70% of cats with DM have been reported to go into spontaneous clinical remission, with good glycemic control. Unfortunately, the glucagon tolerance test is not useful in predicting whether or not a cat is likely to go into remission. In dogs, diabetes mellitus is usually permanent, unless DM occurs secondary to profound insulin resistance, due to hormones such as progestogens and glucocorticoids. This type of diabetes is sometimes referred to as type III DM. In these cases, if the diagnosis is made early and the cause of insulin resistance can be removed, the diabetes may also resolve.
**Poor Response to Insulin**
Clinical signs suggestive of inappropriate response to insulin therapy include recurrence or persistence of clinical signs of DM, disorientation or seizures due to hypoglycemia, an insulin dose higher than 2 U/kg/dose in the dog or > 6 U/dose in the cat, or recurrent ketoacidosis. Adequate assessment of the cause of the problem requires performing a blood glucose curve. Measurement of glycosylated hemoglobin or fructosamine may also be helpful. Once this data has been evaluated, appropriate changes in treatment or further diagnostic testing can then be instituted. In dogs and cats receiving twice-daily insulin, most glucose curves can be performed during working hours (8 am to 6 pm). Common problems that may lead to a poor response to insulin include problems with owner administration, inappropriate insulin dose or formulation, insulin-induced hypoglycemia, rapid metabolism of insulin, and insulin resistance. It is important to take into consideration the level of stress of the patient while in the hospital when interpreting the results of blood glucose curves. It is also important to appreciate that blood glucose curves show significant day-to-day variability. Other factors such as clinical signs, results of urine blood glucose measurements at home, serum fructosamine concentrations, and changes in physical examination (especially body weight), should be taken into account when interpreting the results of a blood glucose curve.

**Problems with Owner Administration**
Diagnosis of problems of owner administration of insulin may be detected either by a thorough history or by administration of insulin from a new bottle in the clinic by a clinician or veterinary technician, followed by a repeated blood glucose curve. Care should be taken to monitor the patient carefully in this setting, however, because severe hypoglycemia can result if the insulin dose has been escalated due to problems with administration. If hypoglycemia does occur, the dose of administered insulin should be decreased by 25–75% depending upon the severity of hypoglycemia and a blood glucose curve repeated after 7 days of the new dose.

**Inappropriate Insulin Dose or Formulation**
In most cases, this diagnosis can be made easily by evaluation of the blood glucose curve. Most dogs and cats require insulin administration twice daily for good glycemic control, so this is the first change to consider if once-a-day therapy is being used.

**Insulin-Induced Hypoglycemia**
Insulin-induced hypoglycemia occurs when excessive amounts of insulin are administered. When the blood glucose concentration drops below 65 mg/dl in response to insulin, compensatory mechanisms drive the blood glucose back into the normal range. These mechanisms include increased glycogenolysis and gluconeogenesis by the liver, and release of catecholamines, glucagon, cortisol, and growth hormone which oppose the action of insulin. As the blood glucose returns toward normal, however, there is not enough insulin present to oppose and dampen these, the effect of these hormones increases, and hyperglycemia may result. Hyperglycemia may persist for hours to days following a hypoglycemic event. Since a spot-check blood glucose or urine measurement performed in the afternoon in such a case may reveal hyperglycemia and glycosuria, increases in insulin dosage based on these measurements may worsen the situation. The diagnosis of insulin-induced hypoglycemia is made by performing a serial blood glucose curve (samples q 2 hours). The condition is treated by decreasing the insulin dose by 25–75%, followed by reevaluation of a serial glucose curve 3–5 days later.

**Rapid Metabolism of Insulin**
Rapid metabolism of insulin refers to a situation when the effect of insulin does not last as long as is necessary to control hyperglycemia for the majority of the treatment period. In most diabetic dogs and cats, twice-daily insulin administration is necessary for ideal glycemic control. In some cases, however, the duration of effect may be only 5–8 hours. This may mean that hyperglycemia is present for a
significant proportion of the day, even when twice-daily administration is instituted. In most cases, clinical signs of hyperglycemia are not present, and no change to therapy is necessary. In some cases an insulin preparation with a longer duration may be necessary. Alternatively, three-times-a-day insulin treatment can be considered.

**Insulin Resistance**

There are many varied causes of true insulin resistance; however, most commonly it occurs due to the effect of excessive concentrations of hormones that oppose insulin. In many cases this is due to the presence of concurrent disease (see Table).

Insulin resistance is defined as peripheral resistance to the effects of insulin such that persistent hyperglycemia occurs despite the administration of > 2.2 U/kg of insulin in the dog or > 6–8 U per cat. Insulin resistance may be caused by a large number of factors.

Progestosterone may be a cause of profound insulin resistance in bitches that are in estrus or diestrus. Exogenous administration of progesterone may also result in insulin resistance. The insulin resistance that occurs is thought to be due to stimulation of growth hormone secretion. Excessive growth hormone secretion and insulin resistance may also occur due to the presence of a growth hormone-secreting pituitary neoplasm. Excessive growth hormone secretion either due to exogenous progestogens (usually dogs) or due to a growth hormone-secreting pituitary tumor (occurs primarily in cats) is called acromegaly. In bitches with insulin resistance due to estrus or diestrus, ovariohysterectomy will result in a rapid resolution of insulin resistance. Treatment for acromegaly relies on removal of the source of exogenous progestogens or treatment of the pituitary neoplasm. The importance of other sex hormones, such as androgens, in causing insulin resistance is not well understood in the dog or cat.

Both endogenous and exogenous glucocorticoids are an important cause of insulin resistance in the dog and cat. Glucocorticoids cause insulin resistance by a number of mechanisms, including increased hepatic gluconeogenesis, decreased tissue utilization of glucose, and decreased cellular receptor affinity for insulin. Insulin-resistant diabetes mellitus is a complication in 10% of dogs with hyperadrenocorticism. The clinical signs of these two endocrine diseases are very similar, so it is important to maintain a high index of suspicion for hyperadrenocorticism (Cushing’s disease) in any case of insulin-resistant diabetes mellitus. Care should be taken when treating these animals for their Cushing’s disease, since their insulin requirement will decrease dramatically as endogenous glucocorticoid secretion decreases.

Insulin resistance may also occur due to hyperglucagonemia in cases of bacterial infection, trauma, congestive heart failure, azotemia, and glucagon-secreting tumors. The resistance resolves once the underlying problem is corrected. Severe renal failure results in insulin resistance due to increased glucagon concentrations, defective transport of insulin into cells, and acidosis. Acidosis decreases receptor affinity for insulin and results in derangements of intracellular glycolysis. Other possible causes of insulin resistance that have not yet been well defined in the dog and cat include obesity, phaeochromocytoma, subcutaneous breakdown of insulin, insulin antibody formation, and post-receptor defects (abnormality of signal transduction within the cell).

**Insulin resistance in dogs and cats (*most common*)**

<table>
<thead>
<tr>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug administration</td>
<td>Drug administration</td>
</tr>
<tr>
<td>(progestogens/corticosteroids)*</td>
<td>(progestogens/corticosteroids)*</td>
</tr>
<tr>
<td>Infection (urinary tract/oral cavity/sepsis)*</td>
<td>Infection (urinary tract/oral cavity/sepsis)*</td>
</tr>
<tr>
<td>Hyperadrenocorticism*</td>
<td>Hyperthyroidism*</td>
</tr>
</tbody>
</table>
Hypothyroidism
Renal disease*
Pancreatitis*
Pregnancy/diestrus*
Pheochromocytoma/glucagonoma
Hepatic disease
Cardiac insufficiency
Hyperlipidemia*
Neoplasia
Severe obesity*
Exocrine pancreatic insufficiency
Antiinsulin antibody excess (beef insulin)

REFERENCES

Drug-Drug Interactions in ICU
Tony Johnson, DVM, DACVECC
College of Veterinary Medicine, Veterinary Teaching Hospital, Purdue University, West Lafayette, IN, USA; Veterinary Information Network (VIN), Davis, CA, USA

- Critical veterinary patients are predisposed to drug-drug interactions (DDI) because of the complexity of drug regimens in ICU and the number of medications used in critical patients.
- Drugs may affect the absorption, distribution, metabolism, and/or elimination of other drugs.
- Toxicity may manifest as increased activity or loss of efficacy.
- Certain pathological conditions seen in ICU patients, such as hypoalbuminemia or organ failure, can alter pharmacologic response.

Protein Binding
One of the most important factors in drug-drug interactions is the plasma protein concentration, specifically albumin. Albumin is the major protein responsible for binding acidic drugs such as warfarin, NSAIDs, and anticonvulsants. Decreases in albumin level, which are commonly seen with critical illness, can lead to an excess of unbound, and therefore more active, drug.

Alpha1-acid glycoprotein (AAG) is the major protein responsible for binding basic drugs such as lidocaine, propranolol, and amitriptyline. As AAG is an acute-phase protein, levels can increase in acute illness and therefore inhibit the actions of these medications.

Hepatic Metabolism
Several sites for drug metabolism exist within the body: liver, kidneys, GI tract, lung, and blood among others. Of these, the liver is the organ that is most important for metabolism and elimination of medications. The cytochrome P450 enzyme (actually a family of enzymes with a complex terminology), which is a lipid membrane-bound hepatic enzyme, is responsible for oxidation, hydrolysis and conjugation of drugs prior to excretion. Certain medications can either inhibit P450 (leading to increased levels of drug that are metabolized by it) or potentiate P450 (leading to increased clearance of drugs that are metabolized by it).

This important enzyme system and its interactions with specific drugs are discussed in more detail below, but drugs and conditions that increase P450 activity include:
- Phenobarbital
- Rifampin
- Early sepsis (due to increased hepatic blood flow)

Conditions and drugs that decrease the activity of P450 include:
- Azole antifungals
- Cimetidine
- Metronidazole
- Omeprazole
- Trimethoprim-sulfa
- Late sepsis
- IL-6
- Tumor necrosis factor-α
RESOURCES
Several online and printed resources exist for comparing drugs and determining safety, although few veterinary resources are available. Human references include the drug interaction calculator available at www.drugs.com and the King Concise Guide to Critical Care Admixtures. The online drug interaction checker allows the user to select the medications that a particular patient is receiving and evaluate them for the presence of DDI. Additionally, the level of threat presented by the DDI is graded from major to minor to facilitate clinical decision-making. The King Guide also makes available a wall-chart that is helpful for displaying graphical information and allows drugs to be visually compared in a matrix format.

An excellent review of the topic was published in Critical Care Medicine 2010 by Papdopolous, et al: Common drug interactions leading to adverse drug events in the intensive care unit: management and pharmacodynamic considerations.

SCIENTIFIC STUDIES
There is a paucity of data in human medicine, and few studies exist regarding DDI. None were identified in a search of the veterinary literature outside of a few lectures given on the topic at academic conferences. Of the few extant human studies, DDI is identified as a significant contributor to ICU morbidity; one study (Ray, Crit Care Med., 2009 Supp1) identified 64% of 400 adult ICU patients as having a potential DDI, of which about 17% had a clinically relevant DDI requiring therapeutic intervention.

A 2007 study in the American Journal of Health System Pharmacology found that 7.5% of human patients admitted to ICU were there for a drug-related event and that half of these were for DDI.

SPECIFIC INTERACTIONS
Metoclopramide and Dopamine
Metoclopramide is a dopamine antagonist antiemetic commonly used in veterinary ICU settings. Dopamine is a synthetic catecholamine used to increase splanchnic blood flow (in cases of acute renal failure and pancreatitis) and as a pressor agent in hypotension. Concurrent use of dopamine and metoclopramide - which could be a common occurrence, as many patients with the above conditions also experience clinically significant vomiting - could result in antagonism of the dopamine and loss of dopamine effect. Although not a particularly dangerous interaction, this is commonly encountered in ICU, and clinicians should be aware of it.

Sucralfate and Quinolones
Sucralfate is a commonly used gastroprotectant. It can form complexes with enrofloxacin in the GI tract, decreasing drug absorption. The risk is loss of efficacy of enrofloxacin. This effect may last for longer than one would think based on the dose interval of sucralfate; human studies have shown poor bioavailability of quinolone antimicrobials even 6 hours after sucralfate administration.

Lidocaine and Furosemide
Hypokalemia secondary to furosemide can blunt the antiarrhythmic effects of lidocaine. Serum K+ should be evaluated in patients with ventricular arrhythmias, and supplementation should be instituted if patients do not respond initially to lidocaine.

Digoxin and Furosemide
Furosemide can increase serum digoxin levels. Furosemide can also cause hypokalemia, which can exacerbate the cardiotoxicity of digoxin, and prerenal azotemia through dehydration, leading to impaired digoxin excretion. Digoxin levels should be monitored closely in patients treated with digoxin and furosemide. Renal values and serum electrolytes should be routinely evaluated during the course of therapy.
Opioids
Opioids are classified by their receptor affinity at any of the several known opioid receptors; most important among these are mu, kappa, and sigma. Opioids that have antagonistic effects at the mu receptor, such as butorphanol, can partially reverse effects of full mu receptor agonists such as morphine and fentanyl, leading to a decrease in analgesic effect. Occasionally this interaction can be used to positive effect; in cases of dysphoria seen with full mu agonists (particularly in cats), butorphanol can partially reverse the negative effects while preserving some of the analgesic effects. The extent of this phenomenon and doses used to achieve partial reversal are a subject of some controversy.

Tramadol and Mirtazapine
Tramadol is an analgesic with opioid-like effects, which has gained recent popularity in veterinary medicine as an agent for oral analgesia for outpatient use. Mirtazapine (Remeron®) is a tetracyclic antidepressant that has appetite-stimulating properties in veterinary patients. Coadministration of tramadol with serotonin-enhancing drugs such as mirtazapine may potentiate the risk of serotonin syndrome, which is a rare but serious toxidrome thought to result from hyperstimulation of CNS serotonin receptors. Symptoms of serotonin syndrome include agitation, tachycardia, hyperthermia, mydriasis, and gastrointestinal symptoms such as vomiting and diarrhea.

Cimetidine
Cimetidine (Tagamet®) is a P450 enzyme inhibitor, and it decreases the breakdown of many drugs as listed above. Other H2 blockers, such as ranitidine and famotidine, are not P450 inhibitors and should be chosen over cimetidine for ICU polypharmacy patients.

Omeprazole and Clopidogrel
Omeprazole is a proton-pump inhibitor that has seen increased use in veterinary patients for various gastrointestinal conditions. It is also a P450 inhibitor, as noted above. Clopidogrel (Plavix®) is an antiplatelet agent that is sometimes used in cases of feline aortic thromboembolism and hypertrophic cardiomyopathy. It is activated to the active form by the cytochrome P450 enzyme system. If the enzyme system is impaired by concurrent administration of omeprazole, then activation of clopidogrel to the active metabolite is decreased, and the risk of thromboembolic disease is increased. Substitution of pantoprazole for omeprazole or an H2 antagonist, such as famotidine, can be used to avoid this interaction.

Ketoconazole and Cyclosporine
Ketoconazole is yet another P450 inhibitor and can decrease the clearance of many drugs. This effect can be used to a therapeutic advantage with cyclosporine, which is a cyclic peptide produced by the fungus Beauveria nivea and is used to treat a variety of immune-mediated disorders, such as perianal fistulae and immune-mediated hemolytic anemia. Administration of ketoconazole with cyclosporine will decrease the degradation of cyclosporine and increase its efficacy. This has primarily a financial advantage, as cyclosporine is often prohibitively expensive.

Doses used for this protocol are:

- Cyclosporine: 4–5 mg/kg/day
- Ketoconazole: 10 mg/kg/day

Cyclosporine serum levels should be evaluated at steady-state (about 1 week). The target level is 500 ng/ml until clinical remission is noted; 200 ng/ml will likely maintain remission.
GENERAL MANAGEMENT GUIDELINE
In order to minimize the occurrence of DDIs, drug regimens should be closely evaluated for all ICU patients. Each new medication added should be evaluated and screened by the clinician to screen for DDI. In critical-care patients, each added drug should have a viable justification. Technicians and, if possible, pharmacists should be involved in screening for DDI and evaluation of the drug regimen. If one is concerned about DDI, various drug references as noted above should be consulted. Knowledge of common interactions and medications involved in DDI can help the veterinary healthcare team avoid iatrogenic complications of therapy.

Communication is key with all team members and pet owners to screen for DDI and manage them if they occur. If a DDI is suspected or confirmed, options for management include discontinuation of the suspected offending medication, switching the medication for a similar medication, or continuation of the suspected medication if the signs are not severe. Patients with suspected or confirmed DDI require vigilant monitoring and followup.

REFERENCES
References are available upon request.
The Critical Kidney: Management of Acute Renal Failure
Tony Johnson, DVM, DACVECC
College of Veterinary Medicine, Veterinary Teaching Hospital, Purdue University, West Lafayette, IN, USA; Veterinary Information Network (VIN), Davis, CA, USA

OVERVIEW
Acute renal failure (ARF) can occur in the hospital setting or at home. Prevention of ARF is very often overlooked as a means of reducing morbidity and mortality. Measures such as IV fluid therapy to offset the hypotension that invariably occurs with anesthesia, avoidance of medications known to have nephrotoxic properties, monitoring renal values and urinalysis of patients on angiotensin-converting-enzyme inhibitors, and performing urine culture on chronic-renal failure patients every 6 months can help prevent the occurrence of ARF.

Therapy for ARF should take a stepwise approach - not all ARF patients will need a diuretic, and not all ARF patients will need dialysis, but some will. Fluid therapy is the starting point and is common to the treatment of all cases of ARF, whether severe or mild, naturally occurring or iatrogenic. If fluid therapy fails to reverse ARF, and volume status is known to be adequate, diuretics (whether of the loop type or osmotic) are the next step. Dopamine, once the hope for bazillions of renal patients, is now on the decline as a therapeutic option. However, some promising therapies are on the horizon, including the calcium channel blocker diltiazem and vasodilators like dopexamine and fenoldopam. Finally, once all medical measures have failed to reverse ARF, dialysis (whether peritoneal or hemodialysis) is indicated.

Key points in management include:
- Correct deficits in hydration, acid-base and electrolyte balance
- Promote volume expansion to induce diuresis and urine production
- Address underlying and secondary factors (such as gastroprotection)
- Avoid complications of therapy (such as fluid overload)

Keeping in mind the “Rule of 20” is a great way to make sure all aspects of therapy for critical patients are covered. This convenient list was developed by criticalist Rebecca Kirby and encompasses all key aspects of caring for any patient - but especially the critical ones, like ARF cases.
- Fluid therapy
- Oncotic pull
- Glucose
- Electrolytes/acid-base
- Oxygenation/ventilation
- Mentation
- Blood pressure
- Cardiac function
- Albumin
- Coagulation
- RBC mass/hemoglobin
- Renal function
- Immune status/antibiotic selection
- GI motility and mucosal health
- Drug dosage and metabolism
- Nutrition
- Pain dosage
- Nursing care
- Wound care
- Tender loving care

**DIAGNOSIS**
The baseline database for all ARF patients should include complete blood count, serum chemistry analysis, urinalysis and urine culture, and venous blood gas/electrolytes. Additional tests may also be indicated, depending on the inciting cause, and include abdominal and thoracic radiographs or ultrasound, leptospirosis serology, coagulation profile, EKG, and possibly tick or fungal serology. Carbamylated hemoglobin is available through some reference laboratories and can help distinguish ARF from CRF for those cases where the time-course of the disease is in question, such as in acute-on-chronic renal failure. Carbamylation of hemoglobin is an irreversible process that occurs in the presence of longstanding azotemia - levels would be expected to be low with acute renal failure and high with acute-on-chronic or chronic renal failure.

**THERAPY**
The initial steps after the diagnosis of ARF is made typically involve simultaneous fluid resuscitation of the patient and instituting the appropriate instrumentation to allow for monitoring and therapy. Placement of a central line, as opposed to a short peripheral IV catheter, allows for copious fluid volumes and hemodynamic monitoring, as well as facilitates sampling. For thrombocytopenic or coagulopathic patients, placement of a jugular line is contraindicated, and therefore a PICC line (peripherally introduced central catheter) can be used. These are typically very long (30–60 cm) catheters that can be placed into the caudal vena cava through the saphenous vein and function as a traditional central line. The risk of thrombotic events and catheter-related sepsis, present with every IV line, is magnified with central lines, and therefore adherence to scrupulous nursing care and sterility is necessary during placement and use of these devices. A radiograph should always be taken after placement to determine proper placement in the vena cava.

Placement of a urinary catheter is also nearly universal in the management of ARF to measure urine output. Due to the increased risk of acquisition of nosocomial pathogens, strict asepsis and nursing care are an absolute must when dealing with these devices, and they should be connected to a closed, sterile collection system. The collection bag should not be raised above the level of the patient at any time, to prevent backflow of potentially contaminated urine into the patient.

Arterial catheters are needed in some ARF patients, particularly if there is concern over respiratory status or vasoactive substances (such as dopamine or dobutamine) are being used. Invasive measurement is the most accurate method of tracking changes in blood pressure.

Fluid therapy is the cornerstone of treatment for ARF. The fluid therapy plan needs to be flexible and well thought out, and it needs to change with the changing needs of the patient. There can be amazing changes in a patient’s volume and hydration status over the course of therapy, and one always must be on the lookout for under-resuscitated or fluid-overloaded patients. **Assessment of urinary output cannot be made until the patient’s hydration deficit has been corrected!**

The initial plan consists of 4 parts:
1. **Initial volume needs if hypotensive** - Usually accomplished in the emergency room before admission to ICU. Up to one full blood volume (90 ml/kg for dogs and 60 ml/kg for cats) is sometimes needed for initial volume resuscitation - although it is prudent to approach these amounts in 1/4 to 1/3 increments to avoid volume overload. Colloids also may be used for rapid volume expansion. Cardiac patients or those with evidence of cardiac pathology (murmurs, arrhythmias, elevated CVP or jugular pulsations) should be very carefully assessed before bolusing fluids, as they are particularly sensitive to fluid overload.
2. **Deficit replacement** - Calculated as percentage estimated dehydration multiplied by the bodyweight (in kg) and administered over 2–6 hours after admission. Typically 5% is the lowest detectable level of dehydration, and severe/lethal dehydration occurs at 12%. Usually replaced with isotonic fluids that have a relatively higher sodium content and lower (or no) potassium when compared to maintenance fluids.

3. **Maintenance** - Typically calculated at 60 ml/kg/d and is divided into 2/3 sensible (mostly urinary) and 1/3 insensible (metabolic and respiratory) losses.

4. **Ongoing losses** - Excessive urinary loss, loss through vomiting or diarrhea, effusions. There is often a massive diuresis as patients enter the polyuric phase of the disease, and this must be replaced with IV fluids or dehydration will ensue.

The initial fluid of choice is 0.9% saline, as it is isotonic, does not contain potassium, and these patients often are sodium depleted through vomiting. There is some concern that the acidity of 0.9% saline (pH 5.6) may worsen preexisting acidosis, but the volume expansion that occurs with fluid therapy typically offsets this effect. Changes to fluid composition and rate as therapy progresses are based on acid-base, chemistry, hemodynamic, urine output, and electrolyte data. Fluid type and composition may need to be changed several times daily, as rapid changes in patient status occur. A burette can greatly facilitate therapy by allowing changes to be made to small volumes of fluid, as opposed to changing the whole bag.

Once patients are urinating well and have entered the polyuric phase, a convenient way of keeping up with urinary losses is to quantify their urine output over a 3- to 4-hour period of time and administer this volume (along with insensible losses for the same time period - typically about 1 ml/kg/hr) over the ensuing 3- to 4-hour time period (as long as there is no sign of fluid overload).

For hypokalemic patients, the sliding scale of Scott is often used as a guide to supplementation.

<table>
<thead>
<tr>
<th>Patient’s $K^+$ (mEq/l)</th>
<th>Amount of $K^+$ to add per liter</th>
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</thead>
<tbody>
<tr>
<td>3.5–4</td>
<td>20 mEq</td>
</tr>
<tr>
<td>3.0–3.5</td>
<td>30 mEq</td>
</tr>
<tr>
<td>2.5–3.0</td>
<td>40 mEq</td>
</tr>
<tr>
<td>2–2.5</td>
<td>60 mEq</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>80 mEq</td>
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</tbody>
</table>

As a general rule, patients should not be supplemented with potassium at a rate to exceed 0.5 mEq/kg/hr, although in severe cases of symptomatic hypokalemia (respiratory weakness, arrhythmias, etc.), this author has exceeded that rule without causing too much death. Hyperkalemia is often encountered in the therapy of ARF, as the kidney is the principal regulator of potassium homeostasis. For moderate hyperkalemia (4.5 mEq/l to 7 mEq/l), fluid diuresis with potassium-free fluids may suffice if urine flow can be established.

For severe hyperkalemia (> 7 mEq/l) or hyperkalemia accompanied by cardiac arrhythmias, several options exist:

- **Insulin and dextrose**: Insulin will promote intracellular potassium uptake, and dextrose can cause endogenous insulin release as well as assuring that hypoglycemia does not occur from the insulin. 0.5 units per kilogram of regular insulin can be given IV, with a bolus of 1 gm dextrose (diluted to 25%) per unit of insulin given. IV fluids can then be converted to contain 5% dextrose to promote further insulin release.
- **10% calcium gluconate**: Does not lower potassium, but exerts temporary cardioprotection through favorably altering transmembrane electrical potentials. Prevents arrhythmias until definitive therapy can lower serum potassium levels. Dose is 0.5 to 1 ml/kg slowly IV while monitoring EKG for arrhythmias.

- **Sodium bicarbonate**: Drives potassium intracellularly in exchange for H⁺. May not work unless the patient is acidic. Dose is 1–2 mEq/kg slowly IV.

I typically mentally divide therapy into three, roughly 6-hour, phases: the first phase where I am filling the void, rehydrating and improving volume status (and honestly, I don’t really give much of a hoot what their urine output is); the second phase, where we begin to hopefully see improvement in output and think about diuretics if output is suboptimal; and the third phase where we are hopefully washed away on a flood of urine.

If urine production is inadequate in the first few hours of therapy (in the range of 0.5 to 1 ml/kg/hr), thought should be given to the patient’s volume or hydration status. As stated above, assessment of renal function and urine output cannot be adequately evaluated until you have rehydrated your patient. If there is no evidence of overhydration, a crystalloid bolus (of 10–20 ml/kg over 20–30 minutes) is a reasonable maneuver to attempt to increase urine output if one suspects a volume deficit. You should see a rise in urine output within an hour if this is going to work. Diuretics are not indicated until their fluid needs have been addressed. If there is truly a volume deficit, CVP should be in the low-normal range (or less than zero). Hypotension, as a consideration separate from volume status, may also be contributing to poor urine output. In this case, blood pressure would be low, CVP would be toward the higher end (5–10 range), and pressor therapy would be indicated. This is a bad place to be and best avoided, as you will be going home late and your patient not at all, most likely.

In any case, an elevated CVP early in the game, coupled with low or absent urine output, is a very bad indicator and associated with a poor outcome.

After 6 hours or so of therapy, your patient’s volume and hydration needs should be met. At this second stage, they may still be above the mythical 0.6 ml/kg/hr threshold (technically they are anuric below this point) but still not be putting out what you are putting in. In this case, where urine output is technically above the oliguric threshold but below your fluid input, they are in a state of relative oliguria. This is the earliest time that the use of diuretics should be considered. Before diuretic therapy is instituted, one should strive to make sure that there are no ongoing losses to account for poor urine output, and that additional fluid boluses are not needed. In this phase, if they are making no urine and have already been volume loaded and treated with diuretics, referral to a tertiary facility for dialysis may be considered.

In the third trimester of therapy, we hopefully have opened the floodgates and they are merrily peeing away, filling bag after bag of liquid sunshine. This is the happy phase. If the ‘ins’ still outweigh the ‘outs,’ consideration should be given to furosemide therapy or mannitol. Furosemide can be administered at doses of 2–20 mg/kg IV every 6–8 hours, starting at the lower end and increasing until you run out of Lasix®. If a response is seen to initial doses, a constant-rate infusion of 0.5–1 mg/kg/hr may be beneficial and offer improved diuresis over intermittent dosing. Mannitol can also be given (0.25–1 gm/kg slowly IV). Mannitol is an osmotic diuretic, mild renal vasodilator, and free-radical scavenger. Because of its strong oncotic effects, mannitol can potentiate fluid overload, especially in the volume-replete patient who is anuric. Since it requires somewhat functional kidneys to metabolize it, it will persist in the anuric patient and draw fluid from the interstitium into the intravascular space. In this case, hypertonic dextrose can be used as an alternative to mannitol at 25–50 ml/kg of a 10–20% solution slowly IV. Absolute anuria at this point warrants referral for dialysis or peritoneal dialysis.

Dopamine has been traditionally used in the management of acute renal failure for its purported renal vasodilatory effects. However, a recent human meta-analysis showed no effect on survival and
only a modest improvement in urine output. Its use is no longer recommended as part of the management of ARF, and is therefore no longer cool. I will, however, still use it if I am desperate, at a dose of 2–20 µg/kg/min CRI. Patients should be monitored for arrhythmias, hypertension, and excitability/seizures.

Monitoring endpoints to aim for during therapy include:
- CVP 8–10 cmH₂O
- Systolic blood pressure > 90, < 180 mm Hg
- Urine output > 1–2 ml/kg/hr (at a minimum), ideally equal to fluid input minus insensible losses

During therapy, dosage adjustments must be made for any medication that is renally excreted (antibiotics, analgesics, antacids). As a very rough rule of thumb, for every 1-point elevation in creatinine above 1, multiply the dose interval by that number. For example, if the creatinine is 3 and you are using a q-12-h drug, it should be administered every 24 hours.

Gastroprotectants are routinely administered to ARF patients due to the lack of renal metabolism of gastrin and gastric hyperacidity. The stress of illness and hospitalization also can contribute to ulcerogenesis. H₂-blocker therapy with famotidine, cimetidine, or ranitidine is often used. For severe cases of suspected or confirmed ulceration, addition of a proton-pump inhibitor such as omeprazole, lansoprazole, or rabeprazole can augment H₂-blocker therapy. Addition of sucralfate to either of the above regimens, if the patient can tolerate oral medication, can complement therapy of severe gastric ulceration.

Antiemetic therapy is often indicated, as uremic gastritis can cause severe and sometimes intractable vomiting. A metoclopramide continuous-rate infusion (CRI) of 1–2 mg/kg/day is an effective way of controlling vomiting. Metoclopramide is a dopamine antagonist and should not be used with concurrent dopamine use, as they will both cancel each other out and the universe, as we know it, will implode at the speed of light. Chlorpromazine is also an effective antiemetic, but its use is limited to normotensive patients, as it can potentiate hypotension. Newer antiemetics such as dolasetron (Anzemet®) and ondansetron (Zofran®) offer improved efficacy but come with a hefty price tag. Combination therapy may also be beneficial for the patient with refractory emesis and continued fluid losses.

Nutritional support should be considered for the ARF patient. If eating, a low-protein, carbohydrate-rich diet such as L/D or K/D should be fed. Anorexic patients should be given liquid diets such as Renalcare® via nasoesophageal tube as a CRI. Persistent vomiting or other inability to use the gastrointestinal tract should prompt consideration of TPN or PPN administered through a dedicated central line.

Patients with suspected or confirmed leptospirosis or pyelonephritis should be administered appropriate antimicrobials, and patients who are suspected of being in pain should receive analgesic therapy.

**MONITORING THERAPY**

Typically, monitoring renal values, electrolytes, and glucose should be accomplished every 4–6 hours during the acute phase of ARF therapy. An I-stat EG8 is a convenient way to assess some of these variables. Acid-base status should be assessed every 6–12 hours depending on the patient’s status, and a full chemistry/CBC run every 24–48 hours to assess overall status.

Physiological monitoring should include:
- TPR every 4–6 hours
- Blood pressure every 4 hours (systolic of 90–180 mm Hg should be the goal)
- Urine output every 2–4 hours
- Body weight every 12 hours
- CVP every 4 hours
  - 0–5 cm H₂O = ‘normal’
  - 5–10 cm H₂O = adequate for ARF therapy
  - > 10 cm H₂O = risk of overhydration

For patients in whom therapy is successful and reestablishment of urine flow occurs, fluids can be gradually tapered over 24–48 hours while assessing all of the above parameters. Patients should be transitioned to SQ fluid therapy, which should be continued for 1–2 months as the kidneys heal.
Emergency Management of Acute Heart Failure

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When managing cardiac failure in the emergency setting, we are often dealing with the management of syndromes and symptoms without necessarily knowing the cause. While a definitive diagnosis provides the best guide for treatment, obtaining that diagnosis (typically through echocardiography) may place an unstable patient at serious risk.

We will therefore discuss the management of cardiac syndromes and then briefly review their causes. We will discuss each of the syndromes separately, but note that they often occur concurrently.

**GENERAL CONCEPTS**

Common syndromes and causes associated with cardiac failure:
- Left-sided congestive failure (L-CHF) - typically due to decompensated valvular disease
- Right-sided congestive failure (R-CHF) - typically due to pericardial effusion
- Low output or “forward” failure - typically due to hypertrophic cardiomyopathy in cats or dilated cardiomyopathy in dogs

**Definitions**
- Afterload: Systemic arterial blood pressure (pressure against which left heart must pump to get blood flow through the systemic vasculature)
- Preload: Ventricular filling pressure (pressure against which blood must enter into the ventricles during diastole)
- Congestive heart failure: “Congestive” implies venous congestion followed by leakage of fluid from the blood vessels into the surrounding tissues, as governed by Starling’s forces
- CVD: Chronic valvular disease

**I. LEFT-SIDED CONGESTIVE HEART FAILURE**

Key clinical signs: pulmonary edema and dyspnea.

**(A) Pathophysiology**
- ↑ Left-atrial pressure due to CVD and valve leakage (backwards flow of blood in systole)
- ↑ Pulmonary venous pressure (hydrostatic pressure)
- → Pulmonary edema

**(B) Clinical Signs**
- Coughing - Usually soft cough compared to tracheobronchial cough. May be productive. If particularly severe, may produce clear to serosanguineous, frothy fluid. Coughing is rarely associated with heart disease in cats.
- Exercise intolerance
- Cyanosis
- Dyspnea - Can be seemingly sudden in onset, particularly in cats, or may be more insidious. Patient may show “air hunger” (standing with head and neck extended and forelimbs abducted). Common complaint is inability to sit or lay down/restlessness. Once asleep, may sleep for protracted periods of time, particularly once pulmonary edema is under control.
- Pulmonary edema
Radiographically, this can appear as a perihilar interstitial (early or mild) to alveolar (late or severe) pattern on radiographs, but it can be highly variable in cats. Appearance in cats can be patchy and not perihilar.

**C** Therapeutic Goals

1. **Decrease left-atrial pressure** (LAP)
   a. Decrease preload (minimizes left-ventricular and hence left-atrial filling pressures)
      i. Diuretics such as furosemide
      ii. Venodilators
   b. Decrease afterload (arterial blood pressure)
      i. Arterial dilators like enalapril and pimobendan
   c. Decrease pre- and afterload
      i. Balanced vasodilators

   **Caution:** An excessive fall in preload through overuse of diuretics can reduce filling pressure below a critical level, thus causing a decrease in ventricular filling and stroke volume. An excessive decrease in afterload can cause weakness and syncope. Excess of both can therefore have detrimental effects on cardiovascular function!

2. **Improve cardiac function** if indicated (i.e., DCM, end-stage CVD)
   a. Improve systolic function
      i. Positive inotropes (dobutamine, digoxin, pimobendan)
      ii. Phosphodiesterase inhibitors (pimobendan)
   b. Improve diastolic function
      i. Slow heart rate (digoxin, beta-blockers, calcium channel blockers)
      ii. Relax heart muscle (calcium channel blockers)
      iii. *Note* - Do not use negative inotropes until after CHF is resolved!

3. **Provide supportive care** until pulmonary edema is under control
   a. Oxygen: Nasal, mask/flow-by, transtracheal, cage
   b. Comfort/pain control: Narcotics, valium, (+/- low-dose acepromazine?)
   c. Cage rest
   d. Nutritional support?

The typical dog presenting for cardiac failure often requires a combination of treatments for L-CHF and low output failure. Typical therapy includes:
- Furosemide at 2–4 mg/kg IV q 2–4 hours as needed
- Furosemide CRI (continuous-rate infusion) can also be helpful and may be more beneficial at resolving edema: 0.1 to 1 mg/kg/hr
- Oxygen support and cage rest
- Sedation (consider morphine or butorphanol)
- If positive inotrope needed/indicated, dobutamine at 5–10 μg/kg/minute IV *initially*
- +/- Sodium nitroprusside at 3–5 μg/minute IV *initially*
- Nitroglycerine paste is not effective for vasodilation
- Refractory cases may benefit from sedation, intubation and postural drainage of edema fluid (mechanical ventilation may also be needed)

Cats are more sensitive to stress and Lasix. A severely dyspneic cat with pulmonary edema might require furosemide IM, sedation, and to be placed in an oxygen cage (and left alone) until it is more stable for IV catheters, diagnostics, etc. Cats are also more prone to accumulation of pleural fluid than dogs and may benefit from immediate thoracocentesis.
II. RIGHT-SIDED CONGESTIVE HEART FAILURE

Key clinical signs: Ascites and/or pleural effusion (the former is more common in dogs; the latter is more common in cats).

(A) Clinical Signs

- Ascites - Distended abdomen, discomfort/restlessness/difficulty sitting/laying. Can cause compromise when severe by pushing on diaphragm and decreasing effective lung capacity
- Pleural effusion - Dyspnea, tachypnea, rarely coughing

(B) Therapeutic Goals

1. Mechanically remove fluid: peritoneal, pericardial, or thoracocentesis
2. Decrease right-atrial pressure
   a. Decrease preload
      i. Diuretics - In RHF, diuretics are the safest means of reducing preload (see important exception below for pericardial effusion).
      ii. Venodilators? - In RHF, venodilators will often decrease right-ventricular filling pressures below critical level. In a failing right ventricle, this critical level occurs at a higher venous pressure. Therefore, venodilators may exacerbate RHF. Dehydration will also decrease right-atrial pressures and have a similar detrimental effect on RV filling.
   b. Increase cardiac output
      i. Positive inotropes - Increasing CO from the right side will also decrease right-atrial pressures. Effective selective pulmonary arterial dilators are not available, and thus positive inotropes are the only available means to increase CO from the right side.
      ii. Fluid support/vascular expansion - particularly with pericardial effusion. IV fluids can make a large difference in cardiac output, particularly if pericardiocentesis cannot be performed immediately. Once tapped, diuretics are rarely required.

The typical case presenting in acute R-CHF often requires some form of centesis, followed by moderate doses of Lasix (1–2 mg/kg 8–12 hours) and a positive inotrope such as digoxin.

**Remember: Always consider pericardial effusion in any animal, especially middle- to old-aged large-breed dogs with signs of acute R-CHF!! Pericardial effusion cases are the one R-CHF in which diuretics and vasodilators are contraindicated, as these drugs will further decrease cardiac output. IV fluids and volume expansion are indicated until pericardiocentesis can be performed.**

Biventricular failure often occurs in the later stages of disease, especially with DCM and end-stage chronic valvular disease. Often patients have a history of L-CHF, but not always. The prognosis is guarded at this stage. Manage the case as above, but note carefully the comments about vasodilators with R-CHF.

III. LOW-OUTPUT CARDIAC FAILURE

Key clinical signs: Weakness, poor perfusion (cold extremities, prolonged CRT).

(A) Pathophysiology

- Pump Failure > systolic dysfunction > myocardial disease
- Decreased cardiac filling > diastolic dysfunction > small chamber size, tachycardia

(B) Clinical Signs

- Exercise intolerance - due to poor muscle perfusion from poor cardiac output
IV. Common cardiac diseases associated with the above-described cardiac syndromes

1. Chronic valvular disease (CVD)
   This is the most common cause of CHF and is usually seen in small and toy-breed dogs. The mitral valve is the most common valve adversely affected. In the early stages of the disease, these patients present with mild L-CHF. This will often be progressive, and animals present to the ER at this stage with decompensated L-CHF. If chordae tendineae rupture occurs, low output failure may also be seen as large volumes of blood regurgitate into the left atrium. This causes an acute rise in left-atrial pressures, often causing peracute, severe L-CHF.

2. Dilated cardiomyopathy (DCM)
   A primary pump failure leading to both low output failure and L-CHF. As the disease progresses, biventricular failure may be seen, thus R-CHF signs may also be seen. Biventricular failure is a poor prognostic indicator.
   a. Canine: Dogs usually present in L-CHF and low-output failure. Often atrial fibrillation is seen. Dogs with advanced disease will often show signs of biventricular failure.
   b. Feline: Cats usually present in low-output and biventricular failure. They often present with life-threatening pleural effusion.

3. Hypertrophic cardiomyopathy (HCM)
   This occurs primarily in cats/rarely in dogs. Cats present with signs of L-CHF due to diastolic compromise. They may show signs of biventricular failure. Dogs with secondary hypertrophy (i.e., due to subaortic stenosis) usually present with ventricular arrhythmias.

(C) Therapeutic Goals
1. Increase cardiac output
   a. Improve diastolic function
      i. HCM
         a) Negative inotropes and chronotropes to relax the heart muscle for improved filling space and slow the heart rate for increased filling times
            (1) Calcium channel blockers (diltiazem) and beta-blockers (propranolol, atenolol) are both negative inotropes and chronotropes
      ii. Pericardial effusion
         a) Pericardiocentesis
         b) *Avoid preload reducers like furosemide until after centesis is performed
         c) May need to increase preload (i.e., IV fluid therapy)
   b. Improve systolic function
      i. Positive inotropes (DCM and CVD)
      ii. Afterload reducers (decreasing peripheral vascular resistance [PVR]) allow increased stroke volume. Remember, SV = systolic pressure/PVR, and CO = HR X SV
2. Treat signs of CHF (see previous sections)
4. **Pericardial effusion**
   Dogs present with signs of R-CHF and low-output failure due to diastolic compromise as a result of extracardiac compression and right-atrial tamponade.

**Other, less common cardiac diseases that cause heart failure syndromes:**
- Congenital anomalies (VSD, ASD, PDA, SAS, tricuspid and mitral dysplasia)
- Parvovirus cardiomyopathy
- Feline endomyocarditis and other feline cardiomyopathies (restrictive, intermediate)
- Heart-based tumors (chemodectoma) and infiltrative cardiac tumors (lymphoma)
- Bacterial endocarditis (rarely, if ever, causes failure)
- Primary arrhythmias
- Boxer cardiomyopathy
- Cocker spaniel DCM (taurine/carnitine responsive?)
Top 10 Pitfalls of Emergency Medicine
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The aim of this monograph is to highlight ten (fairly random) aspects of emergency veterinary medicine that I find to be particularly vexing. Please note that not all are true ‘emergencies’ - no one ever died from lack of a rectal exam. But, these are ten points that I have to constantly remind myself of when dealing with patients - it is a personal catharsis, if you will (even if you won’t). I often present this talk to general practitioners who have to see more of their own emergencies, and I have also given it to groups of veterinary students with an interest in emergency medicine. What I set out to do was provide doctors, present and future, with information I wish that I had when I was starting out in emergency medicine. Even if you are a grizzled veteran of the ER, it is my sincere hope that you will find some nugget of useful information to help your patients and minimize your stress level.

**NUMBER TEN: RECTAL EXAM**
I thought I would start out a little slow. I love to torture interns and students with the old saw: **There are only 2 reasons NOT to do a rectal exam - NO rectum and NO finger.** Evaluation of stool consistency and color (many GI bleeds have been discovered this way), palpation of the prostate and sublumbar lymph nodes are just a few of the physical findings that can be found on rectal exam.

**NUMBER NINE: URINALYSIS AND URINE CULTURE**
OK, we’re still just warming up here, so I didn’t really go with a pitfall, *per se*, but more of a personal pet peeve. I have to admit that I used to be guilty of hardly ever getting a U/A on most patients unless they had ‘I have a urinary problem’ stamped on their forehead. I was happy with the old CBC/Chem, and if they were azotemic I just assumed they were in renal failure. I was naughty. I thought it was a pain to get a U/A; I was afraid of cystos, and my techs hated them, too. In order to adequately assess renal function, you **need** a U/A. Remember - the usual chemistry panel is an insensitive indicator of renal function; 3/4 of nephrons have to be kaput before the renal values start to budge.

Urine cultures also deserve mention. They should be part of the diagnostic workup for unexplained fever, any case of acute renal failure (or acute-on-chronic), and all cases of diabetic ketoacidosis. I try to save a sample for culture any time I submit a U/A. Additionally, all CRF patients should be cultured routinely every 6 months - many will have a low-grade pyelonephritis or UTI that can escape detection on a routine U/A due to the dilutional effects of their PU/PD state.

**NUMBER EIGHT: ENDOTRACHEAL AND TRANSTRACHEAL WASH**
Patients with thoracic pathology (such as suspected neoplasia or infectious conditions like fungal disease or pneumonia) may benefit (at least diagnostically) from this procedure. Simply done and available to the general practitioner, this does not require referral. The notes below are used with permission from Dr. Garrett Pachtinger of the University of Pennsylvania.

- Endotracheal wash is best for small dogs or cats
- Transtracheal washes can be done in medium- to large-sized dogs
- May be falsely negative if antibiotic therapy has already begun
- Do not attempt in patients with severe respiratory compromise

**Approximate injection volume of sterile saline:**

- Cat: 2–3 ml per attempt
- Small dog: 2–4 ml per attempt
- Large dog: 4–6 ml per attempt

**Approach - endotracheal wash:**
- Prior to anesthesia, check to ensure all equipment is accessible.
- Prepare the sterile syringes - After the saline, draw up another 3–5 ml of air into the syringe to help flush in the saline.
- Anesthetize and steriley intubate the patient.
- Once intubated, insert the suction catheter down the ET tube until it cannot pass any farther.
- Flush the saline followed by air down the tube.
- Have your assistant gently coupage the chest, while applying suction to the catheter.
- Immediately after obtaining a sufficient sample for submission, attach the patient to the anesthesia machine to supply oxygen to the patient.
- If you need to repeat the saline flush and aspiration, ideally this should be performed prior to connection of the ET tube to the anesthesia machine to prevent contamination.
- Submit the sample for cytology and aerobic culture, +/- *Mycoplasma* and fungal.

**Approach - transtracheal wash:**
- Clip and scrub the ventral neck.
- Elevate the head and palpate between two rings of cartilage, 3–4 rings below the larynx.
- Locally block this area with lidocaine.
- With the bevel down, insert the needle of the sampling catheter into the skin.
- Advance perpendicular to the trachea into the tracheal lumen between two cartilage rings on the midline of the trachea, feeling a “pop” as you enter the tracheal lumen.
- Raise needle slightly to advance catheter another 2–3 mm toward the lower airways.
- Advance the sampling catheter completely into the tracheal lumen.
- Once inserted, pull the needle back out of the skin and place needle guard on the needle to reduce risk of tracheal laceration, or cutting the sampling catheter that is located in the trachea.
- Inject sterile saline followed by air.
- Coupage the chest and aspirate back on the syringe.
- Repeat as needed.
- Submit sample for cytology and aerobic culture, +/- fungal and *Mycoplasma*.

**NUMBER SEVEN: PNEUMOTHORAX**
Pneumothorax is typically evident through elevation of the cardiac silhouette off of the sternum on the lateral projection, retraction of lung lobes from the thoracic wall, and blunting of the costophrenic angles.

*Thoracocentesis* should be performed bilaterally, generally above the level of the costochondral junction and anywhere from the 6–10th intercostal space (ICS). Because of the presence of the neurovascular bundle caudal to the ribs, the needle should be introduced cranial to the rib. For smaller patients, an 18- to 21-ga butterfly catheter connected to a stopcock and a 20-cc syringe may be sufficient. Larger patients may require a 1½” needle attached to an extension set. Tapping the chest does not generally require sedation or local anesthetic. Any fluid obtained should be saved for analysis (PCV/TP, cytology, culture).

Management of pneumothorax (PTX) can either be very simple or very complex. Some patients with PTX can be managed with a single thoracocentesis, while others will need a thoracostomy tube placed. Decision-making in regards to PTX depends on the number of times the chest must be tapped, the volume of air (or fluid) removed, and patient stability. In general, if the chest must be tapped more than 3 times in a 24-hour period, a chest tube is indicated. Ideally, chest tubes are placed under general
anesthesia and under controlled conditions, but thoracostomy tubes are rarely placed as an elective procedure. Most chest tubes are placed with a combination of chemical and physical restraint and local anesthesia. Chest tube diameter should be roughly equivalent to the diameter of a mainstem bronchus. Chest tubes should enter the thoracic cavity at the level of the 8th ICS and exit the skin at the level of the 10th ICS. This subcutaneous tunnel can be formed by having an assistant pull the skin on the lateral thorax cranially before tube insertion. A routine prep and draping of the lateral thorax is performed, and sterile gloves are worn. A small stab incision is made in the skin, and the chest tube (with trocar) is grasped 2–3 cm from the tip to keep it from advancing too far into the chest. A sharp blow is delivered to the end of the chest tube to place it into the thoracic cavity, and the skin is released to form the tunnel. Alternatively, the trocar can be removed, and the tube tip can be grasped with a pair of Carmalts and bluntly dissected through the chest wall until it is in the thoracic cavity. The tube is then clamped and connected to either a suction apparatus (if continuous suction is needed), or an appropriate stopper is fashioned and the tube is secured to the skin. A Chinese-finger-trap pattern or tape butterflies can be used.

**NUMBER SIX: PERICARDIAL EFFUSION**

This condition is often misdiagnosed as cardiomegaly on thoracic films. Prompt thoracocentesis can make a dramatic impact on a patient’s status. This condition is one that needs to be considered in any geriatric, large-breed dog with a history of collapse, lethargy and weakness. Mucous membranes may be pale, and PCV/TP is often in the normal range. This constellation of clinical signs, while by no means pathognomonic, should prompt an evaluation of the pericardial space. A good discussion of the topic can be found in the proceedings from this conference in 2009: Diagnosis and Treatment of Pericardial Effusion, Western Veterinary Conference 2009; L. Ari Jutkowitz, VMD, DACVECC; Matthew W. Beal, DVM, DACVECC; Michigan State University, East Lansing, MI.

Patients with known or suspected pericardial effusion should not be administered furosemide, as this can cause a disastrous drop in blood pressure and perfusion. Prompt pericardiocentesis, through the cardiac notch on the right side of the chest at the 4th–6th intercostal space, in concert with IV fluid therapy is the initial therapy of choice. Patients should have continuous EKG monitoring and evaluation for recurrence of fluid buildup post-pericardiocentesis. Thorough diagnostic workup would include CBC/chemistry panel and urinalysis, as well as coagulation assays and abdominal and thoracic imaging.

In addition to the clinical signs outlined above, a patient may exhibit jugular venous distension, pulsus paradoxus (diminishing of the palpable pulse on inspiration), or electrical alternans (alternating large and small QRS complexes on EKG), although these findings are variably present and somewhat unreliable. Echocardiography is the diagnostic test of choice, and fluid analysis of the effusion has little diagnostic value unless in-house evaluation demonstrates a supplicative effusion or visible infectious agents; the effusion should be then submitted for bacteriologic analysis. Coagulation status of patients should be assessed before pericardiocentesis. In many cases, the effusion is due to an aggressive malignancy such as atrial hemangiosarcoma, and the prognosis is poor if this can be confirmed as the cause. Other measures that may be indicated include pericardiectomy and/or right atrial appendage removal.

**NUMBER FIVE: ANTICOAGULANT RODENTICIDE**

Anticoagulant rodenticide (hereafter abbreviated AR) toxicity can present in any number of ways, depending on the site of bleeding. Additionally, many pets will present after ingestion but not be showing clinical signs. It is important in these cases to ascertain whether exposure could have occurred in the past or if this is the first possibility of exposure. Additionally, the owners may not be aware (or may not be forthcoming) of a pet’s possibility for exposure. It is important not to rule out AR intoxication because an owner claims that they do not know of any exposure. Patients may show no
clinical signs for several days after ingestion, as it takes time for clotting factors to be used up. ARs inactivate vitamin K1 epoxide reductase, which recycles inactive, vitamin K-dependent clotting factors (II, VII, IX and X) to the active form.

Patients who have ingested an AR within the prior 1–2 hours but have no clinical signs should undergo general decontamination. If there is a possibility of prior exposure, coagulation assays should be run, preferably in-house if available. If there is no possibility of prior exposure and PT/PTT are within normal range, the patient may be treated as an outpatient with 2.5 mg/kg vitamin K1 PO q 12 h for 4 weeks after decontamination and activated charcoal administration. The PT and PTT should be assessed 2–3 days after starting therapy to make sure the dose is sufficient and 2–3 days after cessation of therapy to ensure that they were treated for long enough. Elevated PT/PTT should prompt either a dose increase or extension of the vitamin K.

Patients showing clinical signs of bleeding can have extremely variable clinical signs depending on the site of hemorrhage. Management may include the administration of blood products (such as FFP for replacement of clotting factors, or fresh whole blood or PRBC if there has been significant blood loss), oxygen therapy, and other supportive measures. Fluid therapy may be needed in cases of hemorrhage until blood can be obtained, and crystalloid resuscitation should be titrated to a systolic BP of 90 mm Hg to prevent exacerbation of further bleeding. Thoracocentesis should only be performed in cases where there is confirmed pleural space bleeding and only if there is significant respiratory compromise. If there is documented thoracic cavity bleeding, but the patient is not dyspneic, they should be closely monitored and treated aggressively with plasma and vitamin K. Plasma doses needed for AR intoxication are in the range of 10–30 ml/kg and are usually rounded to the nearest plasma unit size. Very small patients needing plasma should have the unit thawed normally and the initial dose drawn from the unit and administered over 4 hours. The remainder of the unit should be refrigerated and used within 24 hours. Vitamin K1 should not be given IV due to the risk of severe anaphylaxis. If possible, it should be given PO with a meal, as it has superior absorption by this route, and SQ absorption may be diminished in hypovolemic or hypotensive patients.

**NUMBER FOUR: SPONTANEOUS HEMOABDOMEN**

Management of patients presenting with spontaneous (nontraumatic) hemoabdomen presents a challenge. There are many ways to stabilize and diagnose their condition and also assess the extent of their disease; I present only one way of looking at this condition here. While a diagnosis of neoplasia should never be made without histopathological confirmation, studies show that roughly 60 to 75% of dogs presenting with spontaneous hemoabdomen have neoplastic conditions, and the vast majority of these are hemangiosarcomas that carry a poor prognosis (roughly 3 months with surgery alone, 6 months or more with chemotherapy). Counseling of owners is therefore of vital importance when dealing with these cases. (The odds of a neoplastic condition are approximately 50% if a mass is found in the spleen and it is not associated with hemorrhage).

Fluids used for resuscitation of these patients should be carefully titrated, and every effort should be made to keep systolic blood pressure at levels that are sufficient to provide organ perfusion but that will not disrupt forming clots and potentiate hemorrhage. I will try to tailor fluid resuscitation with low volumes of crystalloids and colloids to keep BP near 90 mm Hg and not above if this is possible; avoid bolusing large volumes of fluids without checking BP periodically. Administration of whole blood, if available, should be considered for patients who are going to surgery on an emergency basis. An acceptable alternative is FFP and PRBCs if whole blood is not available. While controversial, an abdominal counterpressure wrap can help slow bleeding and aid in the stabilization of a patient perioperatively, but this can decrease vital organ perfusion. Unfortunately, the decision on when to go to surgery on these patients is often clouded by the availability of a willing surgeon, the status of the patient, available postoperative facilities, and the degree of preoperative workup performed by the
clinician (or desired by the owners). Ideally, thoracic films, coagulation assays, CBC/chemistry panel/urinalysis, and possibly abdominal ultrasound should be considered before surgery, depending on availability and patient status. Additionally, the ideal surgical candidate should have improved hemodynamics prior to surgery, but this may not be achievable in actively bleeding patients. Some patients can be stabilized to allow time to gather the surgical staff and further stabilize the patient (as well as perform a more thorough diagnostic assessment), while others must go to surgery under less-than-ideal conditions, or with a partial workup. If at all possible, different scenarios should be discussed preoperatively with owners so rapid decision-making can be facilitated based on intraoperative findings. Owners should also be counseled about common postoperative complications, such as cardiac arrhythmias, that may prolong the hospital stay.

In patients who are not in pain or dyspneic, hospice care at home is a humane option for those owners who do not wish to go to surgery but are not prepared to euthanize when the diagnosis is made.

**NUMBER THREE: BLOOD PRESSURE**

Adequate organ perfusion occurs when blood pressure is at or near 60 mm Hg mean arterial pressure. This typically correlates to a systolic BP of 90 mm Hg. The three elements of arterial blood pressure are systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP). Systolic arterial pressure is generated by the contractions of the beating heart. Mean arterial pressure reflects the average pressure across the vasculature during the cardiac cycle, and it is therefore the main determinant of organ perfusion. Diastolic pressure is the lowest pressure in the arteries during cardiac filling or diastole.

MAP can be approximated from measured values for SAP and DAP by the following:

\[ \text{MAP} = \frac{\text{SAP} - \text{DAP}}{3} + \text{DAP} \]

**Blood pressure homeostasis.** Several mechanisms work in concert in the normal animal to maintain systemic arterial blood pressure within physiologic range. Both neural and endocrine regulatory mechanisms are determinants of blood pressure, thus any condition that disrupts this internal milieu of the animal can alter blood pressure.

Blood pressure can be expressed by the relationship of cardiac output (CO) to total peripheral vascular resistance (TPR): \( \text{BP} = \text{CO} \times \text{TPR} \)

Cardiac output, in turn, is determined by the heart rate (HR) and stroke volume (SV) in the following way: \( \text{CO} = \text{HR} \times \text{SV} \)

All of these variables, HR, SV, and TPR are the determinants of blood pressure and are the physiological points of control acted on by the various neurohormonal mechanisms used to keep blood pressure within a specified range.

Hypertension is a common entity in the emergency room and ICU; many patients are hypertensive due to their primary disease, and many (perhaps many more) are hypertensive due to fear, pain, or anxiety. My approach to mild to moderate systolic hypertension (in the range of 120 mm Hg to 160 mm Hg) in patients without pathology referable to the hypertension alone (typically acute renal failure, retinal detachment, or seizures) is to look for an underlying cause, such as pain or anxiety, and correct it with analgesia or sedation. Patients with symptomatic hypertension, however, warrant prompt therapy. In cases of severe hypertension (systolic BP > 200 with repeated measurement) or hypertension causing clinical signs, therapy (typically with IV nitroprusside) can be instituted to control BP. This requires ICU-level care and rigorous BP monitoring.
Most cases of mild to moderate hypertension without clinical signs will resolve without direct antihypertensive therapy. Cases where hypertension persists and the patient can tolerate oral meds usually receive either a calcium channel blocker (such as amlodipine), a beta adrenergic blocker (such as atenolol), or an ACE inhibitor such as enalapril. Therapy for hypertension should be undertaken based on known or suspected causes for it; therefore, hard and fast rules for therapy are problematic.

Hypotension is discussed below, but systolic BP should be kept above 90 mm Hg to minimize the deleterious effects of hypotension.

**NUMBER TWO: ANALGESIA**

Many patients suffer in silence, and therapy for pain is problematic. In my experience, many clinicians are afraid of the ‘dysphoric’ effects of opioids in cats, and this is rarely a problem. I also feel that butorphanol is an inadequate analgesic for anything but mild pain - it is overused for severe pain, as can be seen with traumatic injuries. For mild pain, I prefer low-dose hydromorphone or buprenorphine, and for moderate to severe pain I believe a full mu-agonist is indicated. A fentanyl continuous-rate infusion (CRI) of 1–5 µg/kg/hr is an effective and adaptable way of controlling pain, and it can be adjusted to compensate for changes in pain level and sedation. Some cats on opioids (particularly transdermal fentanyl) will develop a fever, although the mechanism for this phenomenon is unexplained. Transdermal fentanyl patches are a popular way of providing pain relief in cats, but I feel that their effect is too unreliable to be a viable option for actual pain. Some patients are oversedated, many are undermedicated, and I feel that they lull the clinician into feeling like they are doing ‘something’ for pain, while in fact they are not. They may be helpful for leveling out the ‘peaks and valleys’ of intermittent opioid administration, but they should not be counted on for complete analgesia.

Sublingual (not oral) administration of buprenorphine (at doses similar to IV or IM use) is a reasonably effective means of providing analgesia to outpatients.

**NUMBER ONE: FLUID THERAPY**

Both as a resuscitative measure and for rehydrating hospitalized patients, fluid therapy is one area I struggle with daily. It seems like no other therapeutic intervention is so fraught with the possibility of either underdoing it or overdoing it - both with potentially disastrous consequences. I will present my approach to fluid therapy - but there are many schools of thought and much controversy regarding this topic. It seems like the temptation exists to just set the pump at ‘two times maintenance’ and call it a day. The actual fluid plan should be calculated out based on an evaluation of the patient and changed to match the changing status of the patient.

For resuscitation of hypotensive or hypovolemic patients, a stepwise approach is usually best (crystalloids >> colloids >> pressors). Provision of external rewarming is vital to restoration of normotension for cats and will help avoid fluid overload.

Crystalloids are traditionally the first line of therapy for treating traumatic shock. The ‘shock dose’ of crystalloids for cats is roughly 60 ml/kg and 90 ml/kg for dogs, which corresponds to one blood volume. This dose should not be delivered all at once, but rather divided into 15–20 ml/kg aliquots and perfusion assessed after each dose. Improvement in mucous membrane color, mental status, body temperature, extremity warmth, urine output and blood pressure (> 90 mm Hg systolic) are indicators that fluid therapy is achieving its goal. One should not rely on one physiological variable alone, but rather an overall assessment of the patient’s status. Resolution of metabolic acidosis, improved central venous oxygen saturation (> 70%), and resolution of hyperlactatemia are also good markers for adequacy of resuscitation. To avoid fluid overload in a hypothermic patient, I will generally try to limit feline crystalloid boluses to 50–75 ml at a time, and administer additional boluses in response to continued hypotension.
If I have reached 50–75% of the calculated crystalloid shock dose without improvement, I will generally administer a colloid bolus. Colloid ‘shock dose’ is 20 ml/kg, but, as with crystalloids, I divide this into aliquots of 5 ml/kg and administer over 5–10 minutes. If I have administered a full crystalloid and colloid bolus, rewarm the patient, and ruled out occult hemorrhage and cardiac disease, pressor therapy is indicated. Ideally, monitoring central venous pressure (CVP) would help guide therapy and avoid over- or under-resuscitation. Patients who are hypotensive with a low CVP (< 0 cm H2O) should be fluid loaded with either crystalloids or colloids (regardless of the dose already administered) until the CVP is in the 0–5 range. **Pressors should not be administered to patients who are not fluid replete**, as ischemia will result. Dopamine (2–20 μg/kg/min), phenylephrine (1–3 μg/kg/min), norepinephrine (0.05–0.3 mcg/kg/min), epinephrine (1 mL of 1:1000 epinephrine per 100 mL of 0.9% NaCl, titrate drip-rate to effect) or vasopressin (CRI dose not established) can be used. Higher doses of catecholamines (such as epinephrine, phenylephrine, norepinephrine) can cause arrhythmias and seizures at the higher end of the dose range in cats.

For true hemorrhagic shock (which is more uncommon than traumatic or distributive shock), replacement of lost volume with type-specific blood products and correction of the cause of hemorrhage are indicated.

For cardiogenic shock, minimal to no fluid therapy is indicated. Rather, diuretic, venodilator (nitroprusside or nitroglycerine), and/or pressor (dobutamine) therapy should be considered. For many cats with hypertrophic cardiomyopathy, in which systolic function is usually normal to supranormal, the development of cardiogenic shock is an indicator of catastrophic myocardial failure and typically cannot be reversed.

Fluid therapy for rehydration in hospitalized patients is a different beast altogether. Once hypotension has been addressed (or in dehydrated patients that present without hypotension), a maintenance fluid therapy plan must be devised. A three-part plan has served me well and helps to match the fluid therapy prescription to the patient’s needs.

Correction of estimated dehydration deficit is the first part and is usually accomplished with isotonic crystalloids and spaced over 6–48 hours depending on patient factors (speed of development, albumin level, cardiac function, etc.). While a dismally inexact science, clinical estimation of dehydration can serve as a guide for this phase of fluid therapy. Levels below 5–7% are generally not appreciable on examination. Patients who are between 7–10% dehydrated generally will have poor skin turgor and tacky mucous membranes. 10–12% dehydration will typically show systemic signs of hypovolemia such as hyperthermia, hypotension, sunken eyes, etc. Hydration deficit greater than 12% is generally considered to have severe metabolic consequences and may be lethal. Remember - these are very rough and inaccurate guidelines. The volume of deficit is calculated as %estimate dehydration X bodyweight (in kg). This gives the volume to be administered over the chosen interval.

The second portion of the plan is provision of maintenance needs. Estimated daily maintenance is 60 ml/kg/day and is provided through isotonic crystalloids. Maintenance fluids are calculated to provide hydration to replace fluids lost through sensible (mostly urinary ~ 30–40 ml/kg/day) losses and insensible (metabolic and respiratory ~ 20 ml/kg/day) losses. Again, much debate exists over the actual numbers for maintenance, and this value should be used as a rough guideline.

The third part of the fluid therapy prescription is provision of fluids to replace ongoing losses. In my experience, this part is often overlooked. Losses exceeding the normal metabolic demands (as outlined above - urinary and insensible) fall into this category. Polyuric patients (diabetes mellitus or insipidus, renal disease, etc.), body cavity effusions (especially through chest tubes and abdominal drains), extensive burns or very exudative skin lesions, GI losses, or hyperthermia all cause losses exceeding those calculated for maintenance fluid requirements alone. For some of these conditions, volumes can be measured and replaced 1 to 1 with crystalloids - for example, thoracostomy tubes or excessive urinary losses. For others, such as vomiting, the volume lost can be estimated and replaced.
Monitoring patient weight can also be helpful in guiding administration of fluids to correct deficits from ongoing losses.
Management of Acute Pain

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INTRODUCTION
The International Association for the Study of Pain proposed the following definition of pain in 1979: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” As veterinarians, we not only have a moral obligation to treat our patients in pain, controlling pain can help avoid some of the negative physiologic effects of pain on the healing process. Untreated pain can cause impaired healing, excessive sympathetic tone and the release of stress hormones - all of which are an impediment to healing. The purpose of these notes and the accompanying presentation is to assist the clinician in the management of acute pain in veterinary patients. I would also like to encourage the practitioner to take a multimodality and preemptive approach to pain management by incorporating some novel techniques and approaches to pain control. Most of these techniques, such as epidural analgesia and CRI analgesia, are relatively easily performed, easy to make profitable, and just plain fun. The end results should be better medicine through advanced pain control.

SCORING PAIN
Pain is a difficult thing to quantify - numerous systems have been developed to adequately assess pain in veterinary patients, but none have gained universal acceptance. In man, the Visual Analog Scale is widely used to rate a patient’s pain, but this approach requires subjective analysis and the ability to communicate. We as veterinarians are left with the inaccurate method of attempting to decide which patients are in pain and which are not through inference. For this reason, we should not rely on any individual variable (such as heart rate, blood pressure, etc.) to make this decision. Rather, we should strive to take an overall approach to assessing pain in our patients, and incorporate all available data into the decision-making process. Physiological variables (HR, BP, body temperature), knowledge of the individual patient’s tolerance for pain and normal demeanor (incorporating owner input where appropriate), and knowledge of the level of pain to be expected for any given surgery or condition should all be rolled into the equation when assessing a patient’s pain level.

PHYSIOLOGY OF PAIN
Transmission of painful stimuli from the periphery to the central nervous system involves a three-neuron chain. Each step in this chain of transmission presents an opportunity for intervention when attempting to address a patient’s pain. The first level occurs when nociceptors (specialized pain receptors that are essentially free nerve endings) are stimulated through mechanical, chemical or thermal means and transmit impulses to the spinal cord. Local tissue variables such as pH, circulation, cytokines and neurotransmitters all play a role in impulse generation and can augment or attenuate the receptor’s sensitivity. Local anesthetics operate at this level by completely blocking nerve transmission through inactivation of fast Na+ channels. In addition, NSAID - and to a lesser degree corticosteroid - administration reduces the concentration of cytokines (such as bradykinin and metabolites of arachidonic acid) which potentiate activation of peripheral nociceptors. Modification of nerve impulses in the spinal cord then occurs as the signals ascend the cord in the spinocervical, spinoreticular and spinothalamic tracts in the dorsal horn, which is the second step in the three-neuron chain. These neurons terminate in the thalamus. Possibilities for pain control at this level include prevention of the ‘wind-up’ phenomenon (amplification of impulses by repeated stimulation) through NMDA-receptor antagonists such as ketamine and amantadine. Finally, impulses radiate from structures such as the
thalamus to higher brain centers where they are perceived. Opioids act centrally through opioid receptors to decrease awareness of painful stimuli.

**Clinical Signs of Pain**

As mentioned above, identification of painful veterinary patients is more of an art than a science. The physical signs of a patient in pain vary greatly amongst individuals, breeds and species. Guarding of a painful area or limb, splinting of the abdomen, loss of appetite, vocalization, aggression or depression may be witnessed by caregivers. Tachycardia, hypertension, and/or hypoventilation can be commonly encountered on physical examination of the painful patient, though some animals with significant intraabdominal pathology (such as pancreatitis or septic peritonitis) may not be tachycardic due to excess vagal tone. The tendency is to treat only those patients who are showing obvious external signs of pain - vocalization, anxiety, aggression, etc. This approach greatly underserves those patients who may be ‘suffering in silence’ - some painful patients respond by withdrawing from their surroundings. For this reason, as in the therapy for pain, using a multimodality approach to the diagnosis of those in pain is beneficial. Perhaps most helpful is the knowledge of those diseases and conditions which are likely to cause pain. This information, along with a patient’s demeanor, physical examination findings, and analysis of physiological variables (such as heart rate, blood pressure and body temperature) can aid in the identification and therapy of painful patients. Recently, pain level has been described as the ‘fifth vital sign,’ a point that underscores the importance of assessing and treating the pain of those under our care.

**Therapy of Pain**

**Opioids**

For acute pain, often associated with trauma, opioids are the most commonly used. Their efficacy and safety make them excellent choices for pain control. Opioids are classified based on their actions at the mu receptor (the receptor subtype responsible for analgesia) as either full agonists (morphine, fentanyl, oxymorphone, hydromorphone, codeine), agonists-antagonists (butorphanol), or partial agonists (buprenorphine). In general, because of concerns of full or partial reversal of analgesic activity, mixing an opioid of one class with another class should be avoided. For example, use of butorphanol in a patient who has received hydromorphone recently may partially reverse the actions of the hydromorphone due to butorphanol’s antagonism of the mu receptor subtype. In some cases, however, this antagonism may prove beneficial - the dysphoria that some cats experience with full agonists can be partially alleviated by low-dose butorphanol. For severe, acute pain, the choice of a full mu agonist is generally indicated, as the level of analgesia provided by either agonist-antagonists or partial agonists is inadequate. Therapy with either of these two latter classes is generally reserved for mild to moderate pain. Butorphanol, in particular, is often overused in pain control. Its short duration of action (1 to 3 hours in the dog, 2 to 4 hours in the cat) and limited potency make it unsuitable for therapy of moderate to severe pain. Side effects of opioids include respiratory depression, histamine release (particularly with IV administration of morphine), hyperthermia, constipation, emesis and panting, and they are generally more pronounced with full mu agonists. Despite this, the fear that many veterinarians have regarding opioid use is unfounded in many cases. Although respiratory depression is a possibility, in many cases (particularly thoracic trauma) patients with adequate pain control will oxygenate and ventilate better than those who have received inadequate pain control. Head trauma patients, as well, present a bit of a challenge when addressing pain control issues. For these patients, respiratory depression potentially can exacerbate intracranial injury, so knowledge of the side effect profile of any opioid chosen is mandatory, as well as monitoring the patient for signs of decompensation (in particular, PaCO₂). Opioids should be given on a fixed schedule (rather than PRN) for the first 24–36 hours following trauma or surgery to avoid a decrease in serum levels and ‘breakthrough’ pain. IV administration avoids
the pain of IM injection and provides rapid analgesia. In some cases, administration of one-half the dose IV and the other half IM is warranted and will result in both rapid and sustained action of analgesia. Preemptive analgesia (administration before onset of painful stimuli such as surgery) greatly decreases the amount of postoperative analgesic required to control pain. Both of these principles highlight the fact that it is much easier to avoid pain than to control it after the fact.

Opioid doses commonly used can be found in the following table.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Feline dose</th>
<th>Canine dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butorphanol</td>
<td>Agonist-antagonist</td>
<td>0.1–1 mg/kg IM, IV or SC</td>
<td>0.1–1 mg/kg IM, IV or SC</td>
<td>q 1–3 h</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Mixed agonist</td>
<td>0.005–0.01 mg/kg IM, IV, or SC</td>
<td>0.005–0.02 mg/kg IM, IV, SC</td>
<td>q 6–12 h</td>
</tr>
<tr>
<td>Morphine</td>
<td>Full agonist</td>
<td>0.1–0.3 mg/kg IM, SC</td>
<td>0.5–2 mg/kg IM or SC</td>
<td>q 3–4 h</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Full agonist</td>
<td>0.05–0.1 mg/kg IM, IV, or SC</td>
<td>0.05–0.2 mg/kg IM, IV or SC</td>
<td>q 2–6 h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Full agonist</td>
<td>1–5 µg IV</td>
<td>1–5 µg IV</td>
<td>CRI or q 1 h</td>
</tr>
</tbody>
</table>

**Local Anesthetics**

Local anesthetics are very useful in therapy for acute pain, and they are incorporated into several techniques used to control pain. Cocaine was the first local anesthetic synthesized, but its use is limited now to the support of Central American dictatorships. Lidocaine’s onset is within 5 minutes, and it lasts up to 2 hours, while bupivacaine will last 6–8 hours but takes 20 minutes to take effect. Toxicity from either drug manifests as neurological signs (tremor, nervousness, seizures) or gastrointestinal signs (typically vomiting) and is generally not seen when doses below 5 mg/kg of lidocaine, and 2 mg/kg bupivacaine are used in dogs (lower doses should be used in cats due to their increased sensitivity to local anesthetics). The “sting” of lidocaine can be avoided by mixing it in a 1:9 ratio with sodium bicarbonate before injection. Lidocaine also has some analgesic properties as a low-dose (25 µg/kg/min) CRI as discussed below.

**NSAIDs**

Nonsteroidal antiinflammatory drugs (NSAIDs) are often avoided in acute pain due to actual and perceived risks with gastrointestinal and renal injury. They are effective and safe analgesics when used in the appropriate patient population; in general, well-hydrated, normotensive patients without preexisting renal or gastrointestinal pathology are good candidates for therapy with NSAIDs. Additionally, NSAIDs should be avoided preoperatively due to potential platelet inhibition. Some of the currently available NSAIDs include carprofen (Rimadyl®), deracoxib (Deramaxx®), tepoxalin (Zubrin®), ketoprofen (Ketofen®), meloxicam (Metacam®), and acetylsalicylic acid (aspirin).

**α-2 Agonists**

α-2 agonists provide profound analgesia and sedation, and, like NSAIDs, are suitable for pain control in carefully screened patients. The α-2 adrenoceptors are presynaptic inhibitory receptors within the sympathetic nervous system and mediate analgesia, anxiolysis, sedation and blood pressure. CNS α2 receptors induce analgesia similar to that mediated by opioid receptors. Stimulation of α2 receptors causes activation of transmembrane (G protein) signal transduction system that ultimately leads to the opening of K+ channels in postsynaptic neurons. The cell then becomes more negatively charged through K+ loss into the extracellular space and hyperpolarized. Since the cell is further from the threshold potential, it is thus more resistant to stimulation. The most common side effect seen with administration of α-2 agonists is hypotension, limiting its usefulness in most critical care and trauma scenarios.
patients. However, it can be a useful adjunct for young, normotensive, otherwise healthy patients needing both analgesia and sedation. One should be aware that the sedative effects of α-2 agonists outlast the analgesic effects. They have the advantage of being completely reversible with specific α-2 antagonists. Addition of 5 μg/kg of medetomidine to an epidural opioid will extend the duration of action of the opioid - in some cases doubling the duration. Xylazine (and its reversal agent yohimbine) and medetomidine (Domitor®), and its reversal agent atipamezole (Antisedan®) are currently the only α-2 agonists available for veterinary use.

CRI Analgesia
Continuous-rate infusions (CRI) of opioid analgesics are an excellent way to ‘even out’ the peaks and valleys of intermittent administration of opioids. Any opioid can be given by CRI - the dose normally given as a single injection is simply divided over the expected dose interval and added to IV fluids or delivered by syringe pump. An initial bolus should be given to raise serum levels until the CRI takes effect. Perhaps the easiest opioid to administer by CRI is fentanyl due to its short duration of action (30 minutes). Doses of 1–5 μg/kg/h are generally used. A combination of morphine, lidocaine and ketamine (MLK drip) is often used perioperatively for painful conditions or procedures. The dissociative agent ketamine, when administered at subanesthetic doses (2–20 μg/kg/min), acts as an NMDA-receptor antagonist and can prevent the ‘wind-up’ phenomenon (amplification of painful stimuli through repeated nerve impulse transmission). As mentioned above, lidocaine at low doses (25 μg/kg/min) has some analgesic properties. A convenient ‘recipe’ for a MLK drip is to mix 8 ml of 15 mg/ml morphine, 1.2 ml of 100 mg/ml ketamine, and 50 ml of 2% (20 mg/ml) lidocaine in 1000 ml of diluent (such as 0.9% sterile saline). This mixture can be run at 1 ml/kg/h and provides 2 μg/kg/min morphine, 17 μg/kg/min lidocaine, and 2 μg/kg/min ketamine. The rate can be increased safely to 3 ml/kg/h without exceeding the dose recommendations for any of the components. 50 ml of diluent must be removed from the bag before mixing to ensure accurate dosing. Various computer spreadsheets have been developed to make CRI analgesia easier - several are available on VIN (www.vin.com), and I would be happy to supply interested individuals with ones in use at our hospital - please e-mail the author at DVMDV8@adelphia.net.

Regional Analgesia
Epidural analgesia and local anesthetic techniques are also very useful adjuncts to analgesic regimens. Local anesthetic techniques such as brachial plexus blockade, mandibular nerve blocks, ring blocks and splash blocks are easily accomplished and do not take specialized materials or skill.

Brachial Plexus Block
Blockade of the brachial plexus provides anesthesia to the forelimb from the digits to the level of the elbow. This technique is easily performed with a minimal level of skill, but should be practiced on cadaveric specimens before attempting it on patients. It is best performed under general anesthesia, usually in conjunction with surgical procedures involving the forelimb, but it can be performed under sedation. Local anesthetic agents are used in this technique.

With the patient in lateral recumbency, an area cranial and dorsal to the point of the shoulder is clipped and surgically prepared. Landmarks for brachial plexus blocks include an area just medial to the point of the shoulder, the first rib and the transverse processes of the cervical vertebrae. With the neck in a natural position, the transverse processes of the cervical vertebrae form a line that traverses the brachial plexus. Two- to three-inch spinal needles work well for brachial plexus injection, while 1½-inch needles may work for smaller patients and cats. In either case, the point of the needle should be inserted so it is at the level of the first rib. The needle should be guided below the scapula but outside of the thorax. Once the desired level has been reached, the syringe should be connected and the needle aspirated to confirm placement outside the thorax and to check for inadvertent placement in a blood
vessel. If air or blood is aspirated, the needle should be immediately removed. After confirmation of proper needle placement, 1–2 ml of the local anesthetic solution is deposited at the point of maximal insertion. Then the needle is slowly withdrawn while simultaneously injecting small amounts as it passes. See Table 2 for drugs and doses.

**Table 2. Drugs for brachial plexus block**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>1 ml/4.5 kg</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>1 ml/4.5 kg</td>
</tr>
</tbody>
</table>

Contraindications to brachial plexus block include coagulopathy, infection in nearby tissues, and sensitivity to local anesthetics. Complications are rare but include inadvertent pneumothorax and intravenous injection.

**Intercostal Nerve Block**

Postthoracotomy patients and chest trauma patients with rib fractures or flail chest benefit from adequate analgesia in order to maximize respiratory excursions without pain. One effective way to provide relief from the pain of thoracic trauma is to block the intercostal nerves. A minimum of 2 rib spaces cranial and caudal to the affected area must be blocked due to overlapping innervation. Intercostal nerve block can be performed in conjunction with surgery or postoperatively under light sedation. Using aseptic technique, the needle is introduced at the caudal aspect of the rib near the level of the intervertebral foramen. Duration generally depends on the local anesthetic chosen, but can control pain for 3–6 hours. The needle should be aspirated to confirm placement outside the thorax and to check for inadvertent placement in a blood vessel. If air or blood is aspirated, the needle should be immediately removed. Contraindications to intercostal nerve block include coagulopathy, infection in nearby tissues, and sensitivity to local anesthetics. Complications are rare but include inadvertent pneumothorax and intravenous injection. See Table 3 for drugs and doses.

**Table 3. Drugs for intercostal nerve block**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>0.25–1.0 ml per site depending on the size of the patient Total dose should be below 8–10 mg/kg</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>0.25–1.0 ml per site depending on the size of the patient Total dose should be below 2 mg/kg</td>
</tr>
</tbody>
</table>

**Interpleural Analgesia**

For patients with a thoracostomy tube, local anesthetic agents can be instilled directly into the chest tube to provide relief of the pain from thoracotomy incisions. Using strict aseptic technique, local anesthetics are placed in the chest tube, and the patient is placed with the incisional side down to allow the agent to migrate to the dependent area. In patients without a chest tube, interpleural catheter kits are available. Care must be taken during the administration of medication to avoid creating a pneumothorax. If possible, chest tubes should not be aspirated for 60 minutes postinjection to allow for adequate contact time. Interpleural analgesia is contraindicated in patients without an intact pericardium due to the risk of cardiotoxicity of local anesthetic agents. See Table 4 for drugs and doses.

**Table 4. Drugs for interpleural analgesia**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>Dogs: &lt; 6 mg/kg q 2–4 h Cats: &lt; 3 mg/kg q 4 h</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>Dogs: &lt; 2 mg/kg initial dose, then 1 mg/kg q 6 h</td>
</tr>
</tbody>
</table>
Cats: < 1 mg/kg initial dose, then 0.5 mg/kg q 6 h

Intravenous Regional Anesthesia
Also known as a Baer block, intravenous regional anesthesia is useful for painful procedures of the distal extremities such as toe amputation, fracture manipulation, bone biopsy, and laceration repair. This technique is simple and can be rapidly performed with materials commonly found in the hospital setting. It is generally done in association with general anesthesia for surgical procedures.

An intravenous catheter is placed in an appropriate vein for the limb undergoing surgery (either the cephalic vein for the forelimb or the lateral saphenous vein for hind-limb procedures). Additional techniques such as a brachial plexus block or lumbosacral epidural can be used in conjunction with intravenous regional anesthesia, but the total dose of local anesthetic must be kept below the toxic dose for each species. Distal placement of the catheter is advised to allow for maximal contact of local anesthetic with tissues. The limb is exsanguinated by application of an Esmarch bandage, starting distally and wrapping tightly in a proximal direction with an elastic material such as Vetrap. A tourniquet is then applied immediately proximal to the bandage, and it must be applied tightly enough to temporarily stop arterial blood flow to the limb. After tourniquet application, the Esmarch bandage is removed and the local anesthetic is slowly injected into the limb. Bupivacaine should not be used in this technique due to its cardiotoxicity when given intravenously. Maximal effect with lidocaine is achieved in 10–15 minutes.

The tourniquet should not be left on for longer than 90 minutes to avoid ischemic damage to the limb, and it should be removed slowly at the end of the procedure to avoid a rapid bolus of lidocaine into the systemic circulation. The tourniquet should be applied tightly to avoid systemic administration of lidocaine before the end of the procedure. See Table 5 for doses for this technique.

Table 5. Intravenous regional anesthesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>Dogs: 2.5–5 mg/kg; volume will depend on the area occluded by the tourniquet</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>Do not use for this technique</td>
</tr>
</tbody>
</table>

Epidural Analgesia
Epidural analgesia is indicated for abdominal surgeries in critical patients, pain control for trauma or patients with intraabdominal pathology (such as pancreatitis or septic peritonitis). Opioids, local anesthetics, and α-2 agonists can all be used epidurally, either alone or in combination. Local anesthetics, which provide total motor and sensory blockade, should not be used in hypotensive or hypovolemic patients due to inhibition of the pressor response. Lipid solubility affects the cranial migration of opioids when administered epidurally. Buprenorphine, which is highly lipid soluble, is less likely to migrate cranially and cause respiratory depression by paralysis of respiratory musculature.

Morphine, in contrast, is the least lipid-soluble opioid and can advance to the thoracic segments of the spinal cord. This can be advantageous if the intent is to provide analgesia for thoracic or forelimb procedures or injury. The lipid solubility of oxymorphone is somewhere between that of morphine and buprenorphine, while fentanyl is highly lipid soluble and unlikely to migrate beyond 1–2 spinal segments away from the site of administration.

Knowledge of spinal anatomy and species differences is necessary in order to successfully and safely perform epidurals. The spinal cord is covered by three membranes: the pia mater, which adheres to the cord itself; the arachnoid layer; and the dura mater. The dura and the arachnoid layer are adhered to each other, and cerebrospinal fluid circulates in the subarachnoid space between the pia and arachnoid layer. The epidural space lies between the bony spinal canal and the dura mater. In man, the spinal cord ends at approximately the level of L1 or L2. In dogs, the spinal cord generally ends at L6–L7,
while in cats it may end as far caudally as S1. For this reason, epidurals in cats must be performed with a great deal of caution to avoid damage to the spinal cord and subarachnoid injection. Incidentally, this is why intervertebral disk extrusion is not generally a neurological emergency in man as it commonly is in chondrodystrophic breeds. A small extension of the meninges and spinal nerves, the cauda equina, extends caudally from the spinal cord. When drugs are placed in the epidural space, they bathe the spinal nerves as they exit the intervertebral foramina and produce analgesia or anesthesia. Inadvertent injection into the subarachnoid space (indicated by the appearance of CSF in the needle hub) warrants a dose reduction of 50% in volume of administered drugs. The extent to which drugs migrate cranially is dependent on factors such as solubility of the agents chosen and volume of injection.

With the patient adequately sedated or anesthetized, either sternal or lateral recumbency is chosen. Materials needed for epidural injection include sterile gloves, drugs to be administered, and an appropriate-sized needle (1- to 3-inch, 18- to 25-gauge spinal needle). Since drugs will migrate to the dependent portion of the spinal canal, the affected side should be placed in the down position if possible. Landmarks for injection include the cranial edge of the wings of the ilia and the dorsal midline. Where these two lines meet overlies the body of L7. Epidural injections are administered just caudal to this point, in the lumbosacral space between L7 and S1. A depression corresponding to the lumbosacral space can generally be palpated, although in very obese patients it may be difficult to find. The site should be clipped from L4 cranially to the caudal sacrum and laterally just beyond the wings of the ilia and surgically prepared. In order to maximally open the lumbosacral space, one should have an assistant extend the pelvic limbs cranially during the procedure. The patient should be moved so the dorsal midline is at the edge of the table and the landmarks confirmed again. With the bevel of the needle oriented cranially, the needle is kept perpendicular to the skin surface and parallel to the floor while it is advanced through the skin. In order to avoid transplantation of skin into the epidural space, it is important to have the stylet correctly positioned within the needle. The depth of needle insertion depends on size of the patient, but a distinct “pop” can be felt as the needle penetrates the ligamentum flavum as it enters the epidural space. If bone is encountered, the needle can be gently “walked” either cranially or caudally until the lumbosacral space is found. In general, misplaced attempts will be cranial to the L7–S1 space. The needle is then advanced an additional 1–2 mm to place the bevel of the needle fully within the epidural space. At this point the stylet can be removed and the hub examined for evidence of CSF or blood, indicating entrance of the subarachnoid space or vertebral venous sinus, respectively. If blood or CSF is encountered, either the procedure can be abandoned or the dose of drugs can be reduced by 50% and given by subarachnoid injection.

Entrance into the epidural space can be confirmed by several methods. Injection of a small amount (0.5–1 cc) of air while ausculting over the lumbar spine (the “whoosh” test), as well as observation of lack of compression of a small bubble of air in the syringe while the injection is administered can be used. Minimal resistance to injection should be encountered if the needle is properly positioned. If the sternal recumbency position is chosen, the “hanging drop” test can be used. In this method, the stylet is removed after the epidural needle has penetrated the skin, and a small drop of sterile saline is placed in the hub of the needle to form a meniscus. Upon advancing the needle and entering the epidural space, the saline will flow into the needle, confirming proper placement.

Keeping in mind the toxic doses for both drugs (approximately 8–10 mg/kg for lidocaine and > 2 mg/kg for bupivacaine), doses are approximately 1 ml of each drug per 4.5 kg (10#) lean bodyweight for pelvic/pelvic-limb analgesia. Larger doses (1 ml/3.5 kg) can be used for abdominal analgesia. Duration of analgesia varies with each drug chosen, but morphine generally lasts the longest (12–24 hours). See Table 6 for doses of each drug. Combinations of local anesthetics and opioids are administered at the same dose as each agent individually. Epidurals should be mixed with sterile saline to a volume of 0.3 ml/kg to a maximum volume of 6 ml. After the epidural is administered, the affected limb should be placed in the dependent position for 20–30 minutes.
Table 6. Drugs useful for epidural analgesia (single injections)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset</th>
<th>Lipid solubility</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>1 ml/4.5 kg (T13–L1)</td>
<td>10 minutes</td>
<td></td>
<td>1–2 hours</td>
</tr>
<tr>
<td></td>
<td>1 ml/3.5 kg (T5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>1 ml/4.5 kg</td>
<td>20–30 minutes</td>
<td>High</td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.1 mg/kg dogs</td>
<td>30–90 minutes</td>
<td>Low</td>
<td>8–24 hours</td>
</tr>
<tr>
<td></td>
<td>0.03 mg/kg cats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>5–20 µg/kg dogs</td>
<td>High</td>
<td></td>
<td>8–18 hours</td>
</tr>
<tr>
<td></td>
<td>5–10 µg/kg cats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>0.05–0.3 mg/kg</td>
<td></td>
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</tr>
<tr>
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<td>4–10 minutes</td>
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<td>6 hours</td>
</tr>
<tr>
<td>Medetomidine</td>
<td>2–5 µg/kg</td>
<td></td>
<td></td>
<td>Extended analgesia ~ 2X</td>
</tr>
</tbody>
</table>

Contraindications to epidural analgesia include coagulopathy, infection at the site of injection, inexperience in epidural injection, and inability to adequately determine pelvic landmarks (for example, very displaced pelvic fractures). Hypovolemic patients should not receive local anesthetics epidurally due to blunting of the physiologic sympathetic (pressor) response. Complications to the procedure are rare but include infection, hemorrhage, excessive motor blockade, hypotension (particularly with local anesthetics), and inadequate analgesia. It has been estimated that approximately 12% of epidural injections do not achieve adequate results.

**Epidural Catheters**

If long-term epidural analgesia is desired, an epidural catheter is an efficient and economical choice for pain relief. The landmarks, positioning and contraindications for placement of a catheter in the epidural space are essentially the same as the technique for epidural injection. Drugs administered epidurally should, in general, be preservative-free, although solutions containing preservatives can be safely used if they are not administered into the subarachnoid space. Astramorph® is a preservative-free formulation of morphine (1 mg/ml) made for epidural use. Buprenorphine does not contain a preservative. If possible, single-use vials should be chosen for epidural use to prevent cross-contamination.

Equipment includes a 17- to 20-gauge, 2- to 3.5-inch Tuohy needle for catheter introduction, a 19- to 24-gauge polyurethane catheter, injection cap, drugs for injection, two pairs of sterile gloves, and bandage material. The Tuohy needles are larger in diameter, stiffer and duller than spinal needles and have an orifice that curves 90° to exit perpendicularly to the long axis of the needle. Many epidural catheters are available in kits that include all materials necessary for catheter placement, such as the Perifix® continuous epidural anesthesia set available from B. Braun Medical, Bethlehem, PA (product code CE-18T), the Arrow Flex-Tip Plus catheter (product code AM-05500), and the Arrow TheraCath (product code AK-05000) from Arrow International, Reading, PA. The cost for epidural catheter kits is generally $12–$35. Positioning is as for epidural injection - either sternal or lateral recumbency. The patient should be surgically prepared and a sterile drape applied over the area. A small hole can be made in the skin with an 18-gauge needle to ease the passage of the relatively dull Tuohy needle. The Tuohy needle is then inserted into the skin with the bevel oriented cranially and advanced until the ligamentum flavum is encountered. The angle of the Tuohy needle for epidural catheter insertion differs from the technique for a single epidural injection in that the Tuohy needle is advanced with a slight craniocentral angle to facilitate catheter advancement. Once the needle is in the epidural space, the stylet is removed and the catheter advanced an additional 2–3 mm to ensure that the bevel is within the epidural space. The hub of the needle should be examined for blood or CSF, indicating entrance of the subarachnoid space or vertebral venous sinus, respectively. The first pair of gloves is then removed, and the catheter is passed through the Tuohy needle to a level that is 1–2 spaces cranial to the desired level.
of analgesia. The catheter should pass with little resistance and should never be pulled back through the needle to avoid the risk of shearing it off within the spinal canal. Once the catheter has been advanced to the desired level, the Tuohy needle is removed and a small “butterfly” of tape is attached to the catheter near the exit site. The tape is then sutured to the skin to prevent migration of the catheter. The exit site should be covered with antiseptic ointment and the area secured with 2-inch x 2-inch gauze and bandage material, if possible. Excess catheter length should be coiled and incorporated into the bandage, as for a jugular catheter.

Strict aseptic technique is a must for prevention of contamination. All injections and connections should be done under aseptic conditions, and any break in sterility should prompt consideration of catheter removal. All ports should be swabbed in alcohol before injection. The catheter site should be frequently assessed for signs of infection. Routine culture of the catheter upon removal has been recommended by many authors and should certainly be done if there is any sign of infection. Epidural catheters can remain in place for 1–2 weeks if tolerated by the patient and no signs of complications develop. All connections should be changed every 2–4 days.

Epidural catheters allow ready access to the epidural space for intermittent injections of analgesics, but they also allow for continuous infusions that may provide superior pain control. A syringe pump is a necessity for continuous-rate infusions. See Table 7 for drugs and doses.

Table 7. Continuous-rate infusions for epidural analgesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine preservative-free without epinephrine</td>
<td>1 ml 3.5 kg followed by 0.1–0.4 ml/kg/hr CRI</td>
</tr>
<tr>
<td>0.0625%–0.125%* (dogs)</td>
<td></td>
</tr>
<tr>
<td>Bupivacaine preservative-free 0.25% with 1 mg/ml preservative-free morphine mixed in a 50:50 ratio by volume</td>
<td>Cats: 0.2–0.5 ml initial dose followed by 0.1 ml/hr CRI</td>
</tr>
<tr>
<td>Dogs: 0.2 ml/kg initial dose followed by 0.025 ml/kg/hr CRI</td>
<td></td>
</tr>
<tr>
<td>Morphine preservative-free (Astramorph), 1 mg/ml</td>
<td>0.3–0.5 mg/kg/day CRI</td>
</tr>
<tr>
<td>Fentanyl preservative-free 50 µg/ml</td>
<td>1–5 µg/kg/hr CRI</td>
</tr>
<tr>
<td>Buprenorphine preservative-free 300 µg/ml</td>
<td>15–60 µg/kg/day CRI</td>
</tr>
</tbody>
</table>

* 0.0625% to 0.125% bupivacaine can be achieved by mixing 1 part 0.25% bupivacaine with 1–3 parts sterile saline or opioid by volume.

**REGIONAL ANESTHETIC/ANALGESIC QUICK REFERENCE SHEET**

**Drugs useful for epidural analgesia (single injections)**

<table>
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<tr>
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</tr>
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<tr>
<td>Oxymorphone</td>
<td>0.05–0.3 mg/kg</td>
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</tr>
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<td>0.001 mg/kg</td>
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</tr>
<tr>
<td>Medetomidine</td>
<td>2–5 µg/kg</td>
<td></td>
<td></td>
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</tr>
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</table>
Continuous-rate infusions for epidural analgesia

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</tbody>
</table>

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Drugs for brachial plexus block

<table>
<thead>
<tr>
<th>Drug</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>1 ml/4.5 kg</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>1 ml/4.5 kg</td>
</tr>
</tbody>
</table>

Drugs for intercostal nerve block

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>0.25–1.0 ml per site depending on the size of the patient</td>
</tr>
<tr>
<td></td>
<td>Total dose should be below 8–10 mg/kg</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>0.25–1.0 ml per site depending on the size of the patient</td>
</tr>
<tr>
<td></td>
<td>Total dose should be below 2 mg/kg</td>
</tr>
</tbody>
</table>

Drugs for interpleural analgesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>Dogs: &lt; 6 mg/kg q 2–4 h</td>
</tr>
<tr>
<td></td>
<td>Cats: &lt; 3 mg/kg q 4 h</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>Dogs: &lt; 2 mg/kg initial dose, then 1 mg/kg q 6 h</td>
</tr>
<tr>
<td></td>
<td>Cats: &lt; 1 mg/kg initial dose, then 0.5 mg/kg q 6 h</td>
</tr>
</tbody>
</table>

Intravenous regional anesthesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 2%</td>
<td>Dogs: 2.5–5 mg/kg; volume will depend on the area occluded by the tourniquet</td>
</tr>
<tr>
<td></td>
<td>Cats: Do not use for this technique</td>
</tr>
<tr>
<td>Bupivacaine 0.5%</td>
<td>Do not use for this technique</td>
</tr>
</tbody>
</table>

REFERENCES

**Feline Hepatic Failure - Management of Common Complications**
Tony Johnson, DVM, DACVECC
College of Veterinary Medicine, Veterinary Teaching Hospital, Purdue University, West Lafayette, IN, USA; Veterinary Information Network (VIN), Davis, CA, USA

**INTRODUCTION**
Hepatic failure is a relatively common entity in emergency and critical care medicine and presents some unique challenges in terms of diagnosis and therapy. This monograph will cover primarily therapeutic options for dealing with the most common complications seen in association with hepatic failure in dogs and cats. Coagulopathy, hepatic encephalopathy, general supportive measures, and nutritional support will be discussed.

**HISTORY AND PHYSICAL EXAMINATION**
The history can provide important information to assist the clinician with making a proper diagnosis and providing the family with prognostic information. An acute process has the potential for complete recovery due to the liver’s remarkable regenerative process; the liver will fully regrow and recover function even if 80% of the parenchyma is damaged. However, chronic processes that have gone undetected may have progressed to the point that a guarded to poor prognosis is warranted due to extreme loss of hepatocytes. Additional historical information that is important to obtain includes access to toxins (such as xylitol or acetaminophen), travel history, and access to medications.

Common physical exam findings that provide evidence for hepatic failure include signs of hepatic encephalopathy (such as altered mentation, blindness or salivation), coagulopathy (such as melena, pale mucous membranes or purpura), icterus, ascites (which may be due to low oncotic pressure and hypoalbuminemia or neoplastic effusion), or indications of an infectious process such as a fever. Additionally, the patient’s hydration status or need for urgent fluid resuscitation should be evaluated.

**DIAGNOSTIC TESTING**
While an in-depth discussion of the diagnosis of hepatobiliary disease is beyond the intended scope of this monograph, the following information presents a review of the major diagnostics used in patients with liver disease.

**Initial Database**
A CBC, biochemistry panel and urinalysis should be performed on all patients with suspected or confirmed hepatic disease. Common biochemical abnormalities found in patients with hepatic disease include elevated ALT (indicative of hepatocyte/parenchymal damage), elevated ALKP (indicative of cholestasis) and elevated total bilirubin (which can be due to cholestasis or hemolysis most commonly). Other enzymes that can be elevated include AST, which is found with marked cellular necrosis, and GGT, which is a membrane-bound enzyme associated with bile duct epithelium and disorders of the biliary tree.

Patients with hepatic failure have evidence for severe functional derangement of the liver to the point that it cannot perform some of its more important functions: the production of albumin and glucose. Since urea is synthesized by the liver, a low BUN is also indirect evidence for hepatic failure.

CBC may reveal evidence of infection/inflammation (leukocytosis with or without a left shift), anemia (from GI bleeding or chronic disease), neoplastic leukocytosis, or it may be normal. There are no specific findings on the hemogram with hepatic disease. If DIC or a coagulopathy is present, thrombocytopenia is a common finding.
Bilirubinuria is a common finding in patients with hepatic disease or failure, and it should be interpreted in light of the patient’s serum bilirubin level. A small amount of bilirubinuria is a normal finding in male dogs, especially with concentrated urine.

Other abnormalities noted may assist with overall assessment of the patient’s hydration status, and any concurrent diseases present, such as renal disease. Dogs with concurrent renal and hepatic disease should be tested for leptospirosis and started on penicillin-class antibiotics. Appropriate precautions should be taken to avoid contact with urine and potential zoonotic transmission of leptospirosis.

For most patients with hepatic disease, abdominal ultrasonography is a helpful aid in making a diagnosis (although it is rarely sufficient alone to arrive at a definitive diagnosis). Evaluation of the gallbladder, biliary tree and echotexture of the hepatic parenchyma can help narrow the focus of future testing. Definitive diagnosis often requires a hepatic biopsy, which can be complicated by the coagulopathy that often accompanies hepatic failure.

Similarly, radiographs can demonstrate hepatomegaly (seen with infiltrative processes like lymphoma) or microhepatica (seen with chronic processes or portosystemic shunts).

**Expanded Database**

Thoracic radiographs are a helpful adjunct in patients with suspected or confirmed neoplastic disease. Three-view (right- and left-lateral, VD views) should be obtained to maximize diagnostic yield.

As previously mentioned, serology for infectious agents can be considered based on the results of the initial database. Leptospirosis (dogs) and toxoplasma (cats) titers can be submitted to commercial laboratories.

For a definitive diagnosis, many hepatic diseases will require a biopsy. Less invasive means, such as aspiration, can also yield useful results but run the risk of false negative answers due to small sample size. Needle aspirates of inflammatory conditions (such as cholangiohepatitis), hepatic lipidosis and hepatic lymphoma have a reasonable degree of success. Many patients with liver failure will present with a coagulopathy, which will obviously make invasive diagnostics a risk for the patient. Management of coagulopathy is discussed below.

Biopsy samples can be obtained through minimally invasive means (such as laparoscopy or Tru-Cut, ultrasound-guided biopsy) or through laparotomy. Any samples obtained should be submitted for culture and sensitivity in appropriate media if an infectious process is suspected, or in formalin for histopathology.

For patients with anemia or scheduled for invasive diagnostics, a coagulation profile (PT/PTT) is warranted. There is a great deal of variability in results, however, so results should be interpreted in light of the patient’s overall status.

Patients with hepatic encephalopathy often have elevated ammonia levels, and many in-house laboratory machines are capable of running this analysis. Management of hepatic encephalopathy is discussed below.

**Conditions to Rule Out**

As for diagnostic testing, an exhaustive list of all diseases that can affect the liver is not the intention of this lecture. An abbreviated list of conditions is presented below to assist in formulating the initial diagnostic and therapeutic plan.

- **Toxins:** Acetaminophen, xylitol, aflatoxin, many others
- **Infectious:** FIP, leptospirosis, cholangiohepatitis, toxoplasmosis
- **Neoplasia:** Lymphoma, hepatocellular carcinoma, mast cell tumor
- **Inflammatory/Immune-mediated:** Chronic active hepatitis, cirrhosis, autoimmunity
- **Extrahepatic biliary obstruction (EHBDO):** Pancreatitis, calculi
- Portosystemic shunts

**GENERAL THERAPEUTIC PRINCIPLES**

**Fluid Therapy**  
Most patients with hepatic disease will present with some degree of anorexia or dehydration, and many patients will benefit from inpatient therapy with IV fluids. Lactated Ringer’s solution should be avoided, as the lactate is metabolized in the liver and may contribute to a metabolic acidosis. Fluid therapy plans should incorporate information from the initial database, history and physical to come up with a plan that is tailored to the patient’s needs. Simply placing a patient on ‘two times maintenance’ is not sufficient, and the patient should be frequently reevaluated to determine needs for changes to the fluid prescription.

Some patients will have deficits in interstitial and intracellular volume (dehydration) as well as intravascular volume. Many of the patients with intravascular volume deficits will be tachycardic and/or hypotensive and may benefit from rapid volume expansion with either isotonic crystalloids (such as Normosol-R) or colloids. Boluses of fluids should be titrated in 1/4 to 1/3 shock volumes (90 ml/kg in dogs, 60 ml/kg in cats) to obtain a systolic BP of > 90 mm Hg. Fluids should be given with great care in bleeding patients (to avoid disruption of blood clots) and hypothermic cats (to avoid fluid overload).

Patients who are hypotensive despite fluid therapy may benefit from pressor support with synthetic catecholamines such as phenylephrine (1–3 µg/kg/min) or dopamine (5–12 µg/kg/min). These very potent vasoconstricting drugs must be administered via continuous-rate infusion (CRI) and require 24-hour care. Ideally, CVP should be in the normal range (5–10 cmH2O) to ensure adequate intravascular volume prior to starting pressor therapy. Pressors should not be administered to hypovolemic patients, as they will worsen ischemia.

**Electrolytes**

Electrolyte needs should be based on the initial database and serial lab tests. Any patient on IV fluids should have electrolytes evaluated at least daily, with particular attention paid to sodium and potassium levels. Patients on replacement crystalloids for several days (such as Normosol-R) tend to accumulate excess sodium, and consideration should be given to switching to a maintenance fluid (such as Normosol-M) after initial volume and dehydration deficits have been corrected. Hypokalemia should be replaced with IV fluid supplementation. The sliding scale of Scott can help determine the amount of KCL to be added to 1 L of fluids for those patients who have fluids running at maintenance rate:

<table>
<thead>
<tr>
<th>Patient’s [K]</th>
<th>Amount of KCl to add to 1 liter</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3.5 mEq/L</td>
<td>20 mEq/L</td>
</tr>
<tr>
<td>3.0–3.5</td>
<td>30</td>
</tr>
<tr>
<td>2.5–3.0</td>
<td>40</td>
</tr>
<tr>
<td>2.0–2.5</td>
<td>60</td>
</tr>
<tr>
<td>&lt; 2.0</td>
<td>80</td>
</tr>
</tbody>
</table>

Alternatively, K+ can be supplemented between 0.1 to 0.5 mEq/kg/hr for several hours and rechecked. **0.5 mEq/kg/hr (called KMax) is the upper limit for K+ supplementation** and should not be exceeded due to the risk of cardiotoxicity.

Patients with hypokalemia refractory to potassium supplementation should be assessed for hypomagnesemia, as magnesium is a cofactor for potassium metabolism and uptake.
Hypoalbuminemia/Anemia

Oncotic support is of great importance in patients with edema and/or hypoalbuminemia. Ideally measurement of colloidal oncotic pressure (COP) should be used to guide therapy, but this is not widely available. Normal COP is 17–30 mm Hg, and the COP of hetastarch is 30 mm Hg.

Human albumin can be used in hypoalbuminemic patients with edema. The discussion of human albumin must be prefaced with a statement that its use is considered controversial by many. Concentrated human albumin solution typically contains 20 or 25% albumin (200 or 250 mg/mL). By contrast, whole blood and plasma contain about 2.5% albumin; thus, they will not increase intravascular COP or albumin as effectively and will require higher volumes.

Plasma can be used for albumin replacement and oncotic pressure support at a dosage of 20 to 30 ml/kg, but the volumes needed can risk volume overload and incur considerable expense. Concentrated 25% albumin may be the more appropriate colloid for resuscitation in patients with symptomatic hypoalbuminemia, particularly in postoperative or septic critical care patients.

Cats should always be blood-typed and cross-matched prior to any blood product administration (human serum albumin does not require blood typing for cats). Plasma may still contain enough red blood cells to cause serious or fatal transfusion reactions. Transfusion of type A blood into a type B cat typically results in a fatal transfusion reaction.

Simply replacing albumin because the measured value is low is not indicated in the absence of clinical signs, and it exposes the patient to unnecessary risk. If possible, nutritional support (see below) via enteral or parenteral nutrition is the preferred means for normalizing serum albumin.

The albumin dose for transfusion of concentrated albumin solutions can be calculated through the following formula:

- Calculate the total body plasma volume in deciliters - 4.5% of bodyweight (kg) x 10.
- Calculate the total plasma albumin in grams (patient and target value) - this is the patient’s measured serum albumin level x plasma volume, as well as the desired albumin level x plasma volume (typically a value of 2 g/dL is sufficient for a target level).
- Calculate the plasma albumin deficit; this is the difference between the patient’s albumin level and the target level.
- Since only 40% of the total body albumin resides in the vascular space (60% is interstitial), divide the plasma albumin deficit by 0.4 to obtain the total body albumin deficit in grams.
- Calculate the volume of albumin needed, given that 1 ml of 25% albumin contains 250 mg of albumin. This is equivalent to multiplying the albumin deficit in grams by a factor of 4 for 25% and a factor of 5 for 20%.

As a general rule, administration of 1 mL of whole blood per kg bodyweight will raise the PCV by 1%. Thus for a rise of 10%, one would administer 10 mL/kg whole blood. PRBC can be dosed at 75% of the whole blood dose, because they have a higher PCV.

Risks of using concentrated human albumin and blood products are allergic transfusion reactions and volume overload. Signs of mild allergic transfusion reactions may include fever, vomiting, urticaria and facial swelling. More serious transfusion reactions include acute respiratory difficulty, hypotension and circulatory collapse. Urine, serum, or plasma can show signs of hemolysis. Fatal reactions to mismatched blood products can and do occur, particularly if a type B cat is administered type A blood. Delayed reactions up to several weeks later have also been reported with human albumin administration. Patients receiving blood transfusion should have capillary refill time (CRT), mucous membrane color, temperature, pulse rate, and respiratory rate monitored initially every 15 minutes during the first hour of administration, then hourly until the transfusion is completed.
When side effects do occur, the transfusion should be immediately discontinued, and additional therapy considered, such as diphenhydramine (1–2 mg/kg IM) for mild reactions. Fast-acting corticosteroids, such as dexamethasone sodium phosphate (0.1 to 0.2 mg/kg IM or IV), may be used for severe transfusion reactions, but they are generally not needed for milder reactions. An assessment should be made to determine if there is a continued need for blood products but at a slower infusion rate. Reevaluation of donor compatibility through further cross-matching should be considered. Due to the possibility of bacterial contamination of blood products, submission of a sample for bacteriologic testing should be considered. Pretreatment with corticosteroids or antihistamines is not routinely indicated unless a patient has experienced a transfusion reaction in the past.

Coagulopathy
Because of the liver’s role in synthesizing clotting factors, it is common to be faced with coagulopathic patients. Patients with a coagulopathy on paper must be treated differently from patients who need to have invasive diagnostics performed or have evidence of active bleeding. Additionally, in order for a coagulopathy to be clinically significant, coagulation values greater than 25% above the high end of normal may require therapy. PT and PTT should be assessed in any patient with a decreasing hematocrit and prior to any aspirates or biopsies.

If a coagulopathy is documented, administration of vitamin K1 should be considered at 2.5 mg/kg SQ or orally. IV administration is not recommended due to the risk of anaphylaxis. Additionally, plasma should be considered at 6–10 ml/kg to replace clotting factors. Plasma may need to be given every 8 hours or as a CRI in some cases. Guidelines for blood typing are outlined above.

Hepatic Encephalopathy
Patients with liver disease and altered mentation (coma, seizures) should be suspected of having hepatic encephalopathy (HE). The exact pathophysiology of HE is poorly understood, but it involves 1) cerebral toxin accumulation (ammonia, mercaptans, short-chain fatty acids, manganese, gamma-aminobutyric acid (GABA), and false neurotransmitters); 2) alterations in plasma amino acids that impair normal cerebral function; and 3) increased cerebral sensitivity to toxins.

The key points of managing HE include:

- Protein restriction
- Lactulose administration
- Penicillin-class or metronidazole antibiotic therapy, aimed at diminishing the number or activity of GI bacteria that produce ammonia. Lactulose helps in promoting GI tract emptying and also provides an alternate substrate to GI flora that results in less ammonia production than other nutrients. Lactulose can be given PO to patients who will tolerate it, via NE or NG tube or via retention enema at a dose of 1–5 ml (total dose) every 6–8 hours. A cleansing enema with warm, soapy water, iodine or DSS can also be performed to reduce bacterial load.

If patients are eating, a limited-protein diet, such as Hill’s K/D or L/D, should be fed. Patients with an NE/NG tube should receive CliniCare RF, and patients on parenteral nutrition should receive a low-protein formulation.

Administration of a penicillin-class antibiotic, such as ampicillin or ampicillin-sulbactam (Unasyn®) (22 mg/kg IV q 8 h) or metronidazole (7.5 mg/kg IV q 8 h), will help decrease bacterial numbers and also may aid in primary therapy for infectious causes of hepatopathy.

Gastroprotection
Ulceration is common in patients with hepatic disease, and digestion of blood can contribute to HE. Patients with a hepatopathy should receive gastroprotection with sucralfate and H2 blockers such as famotidine or ranitidine. Cimetidine should be avoided due to its hepatic metabolism. Vomiting can be
controlled with a metoclopramide CRI at 1–2 mg/kg/day in fluids. Maropitant should generally be avoided in patients with liver disease. 5HT3 receptor antagonists, such as ondansetron, may be helpful in controlling vomiting.

**Nutritional Support**
Patients that have not eaten for 3–5 days are candidates for aggressive nutritional support.

**APPETITE STIMULANTS AND FORCE-FEEDING**
When the prospect of inpatient treatment for nutritional support is discussed with owners during a consultation, many inquire about appetite stimulants such as cyproheptadine and mirtazapine. While it is true that these medications have averted the need for aggressive nutritional support in some patients, they often delay appropriate nutritional intervention until catabolism has progressed and the side effects of prolonged anorexia and malnutrition have become very advanced. In addition, these medications may have undesirable side effects (such as sedation or dysphoria in cats with cyproheptadine, hepatic necrosis with oral diazepam, and sedation and hypotension with mirtazapine), which can further compromise patient care. For these reasons, it is important to limit the use of appetite stimulants to a short trial in patients who have not experienced a prolonged (> 3- to 5-day) period of anorexia, or to those cases where other alternatives have been declined due to cost after appropriate owner education. For patients that require hospitalization, the use of appetite stimulants should be reserved for those patients that are already recovering from their disease and simply need a little help jumpstarting eating. Appetite stimulants can also be used to determine if patients can tolerate oral feeding before being discharged home. It is also important to realize that inappetence is never a disease in its own - it is always secondary to another problem. Therefore, the use of appetite stimulants as the sole therapy for anorectic patients is never appropriate.

Force-feeding deserves special mention, as it not only is unlikely to provide sufficient nutrition to meet patient needs, the sheer struggle associated with it can lead to an uncooperative patient (who becomes more difficult for all therapeutic interventions), and, more importantly, it can lead to a food aversion and worsen the patient's chances of eating on its own. This problem can be particularly pronounced in cats. There is also a risk of aspiration pneumonia in debilitated patients or those with pharyngeal dysfunction (e.g., laryngeal paralysis). While it may be tempting to try this tactic, it should be avoided and another method of providing nutrition sought.

**TUBE FEEDING**
Selecting one tube type over another has as much to do with individual skills, preference and comfort level as it does with patient factors.

In some patients with liver disease, nutritional support can be reasonably expected to be of a short-term (3–5 days) nature. Additionally, some patients may not be ready for a more invasive form of tube placement. For these patients, who are generally treated as inpatients, a nasoesophageal (NE) tube is probably the most expedient way to provide EN. Inexpensive, relatively well-tolerated and easily placed without specialized equipment, NE tubes can easily be incorporated into the treatment plan for every clinician. The advantage that NE tubes have over nasogastric (NG) tubes is maintenance of function of the lower esophageal sphincter (LES) and the prevention of reflux esophagitis: NG tubes will interfere with LES function and permit erosive esophagitis through potential reflux of gastric secretions. NG tubes, however, will permit the decompression of the stomach in cases of gastroparesis and allow fluid to be suctioned off, which is not possible with an NE tube.

Both pharyngostomy and esophagostomy tubes can be used in outpatients for longer-term (days to weeks) provision of EN. The larger diameter of these tubes will allow for the use of thicker diets without dilution. Strained and blenderized diets (such as L/D) can also be used with caution, due to the risk of tube occlusion. These tubes are well tolerated and can be safely and easily placed as an
outpatient procedure in cardiovascularly stable patients with brief sedation. Esophagostomy tubes tend to be better tolerated since they avoid any intrusion on the pharynx - their placement is discussed below. Similar to NE and NG tubes, these tubes are relatively contraindicated in coagulopathic patients due to the risk of local bleeding, and they are also relatively contraindicated in patients with severe esophageal disease, depending on the clinical severity. Feedings can commence immediately after placement.

**Gastrostomy** tubes (or G-tubes), which are typically placed endoscopically, can be left in place for many months if needed and can provide total nutritional support. They require a moderate level of skill for placement and require specialized equipment (either an endoscope or specialized placement device) and general anesthesia. G-tubes can also be placed during laparotomy or laparoscopically. They are often better tolerated than esophagostomy or pharyngostomy tubes. Once placed, they should be left in for a minimum of 14 days to allow a mature fibrin seal to form along the tube tract between the serosa of the stomach and the peritoneum and minimize the risk of leakage. Patients with peritonitis, hepatic disease, or hypoalbuminemia, or patients who are undergoing aggressive chemotherapy or are otherwise immunosuppressed are at risk for complications, and tube placement should be undertaken cautiously with an informed owner due to the risk of leakage of gastric contents. G-tubes are easily utilized at home by pet owners with a high degree of success. Feedings can generally commence within 12–24 hours of placement - enough time for an initial fibrin seal to form.

Based on tube diameter, either a liquid diet or syringeable paste-consistency diet is chosen. When using tubes of less than 12 French, liquid solutions must be used. With larger tubes (ideally 18 French or larger), blended canned food can be used. Most commercially available liquid diets (such as CliniCare RF) have a caloric density of 1 Kcal/mL.

The food is allowed to come to room temperature (if refrigerated), but microwaving should be avoided to reduce the risk of thermal injury.

Once the daily amount of required Kcal has been calculated (based on \((BW(kg) \times 30) + 70\)) and the required volume of diet known, the feedings can be divided into a number that can be accomplished at home or in hospital. Generally the first 3 days after tube placement, feedings are smaller and gradually approach 100% of RER. For NE and J-tubes, CRI feedings can be undertaken with a syringe pump or fluid bag and fluid pump. Feeding every 4–6 hours for inpatients and every 6–8 hours for outpatients is usually advised.

**Tube Placement - Nasoesophageal/Nasogastric**

NE and NG tubes can be generally placed in awake patients. Fractious animals may require procedural sedation with an alpha-2 agonist (in cardiovascularly stable patients), neuroleptanalgesia (combination of a sedative such as acepromazine and an opioid) or propofol.

The largest tube that can usually be placed in a cat’s nose is an 8 French tube. (French size divided by 3 is equal to the outer diameter of the catheter in millimeters, so a 9 French tube has an outer diameter of 3 mm.) Tubes of 8–10 French can be used in dogs if they are of appropriate length.

The tube should extend to just proximal to the 8th–10th rib to avoid entry into the stomach. The 13th rib is identified and the tube measured and marked to correspond to the 8th–10th rib.

Two to three drops of topical local anesthetic (such as proparacaine) are instilled into the intended nostril. With the patient in sternal recumbency and the patient’s head in normal position, the tube is directed ventrally and medially in an attempt to cause the tube to enter the ventral meatus. If the tube is introduced and meets resistance after passing a short distance, it has likely passed into the dorsal meatus and is abutting on the cribiform plate. Some patients can be observed to swallow as the tube enters the pharynx. If the patient begins coughing, the tube may have inadvertently entered the trachea. Once the length marks have been reached, the tube is secured to the lateral aspect of the muzzle with tape butterflies and suture.
Tube placement can be confirmed by several methods:

- A lateral radiograph
- Attaching a syringe and aspirating on a properly placed NG tube will produce negative pressure as the side of the esophagus will be sucked against the tube. A tube placed in the trachea will continue to draw air.
- Attaching an end-tidal CO₂ (ETCO₂) monitor to a properly placed tube will read zero (there is minimal CO₂ in room air), while one attached to one that has been inadvertently placed in the trachea will detect CO₂.
- In most awake patients, injecting 2–3 cc of sterile water or saline will stimulate a cough if the tube has been inadvertently placed in the trachea.

**Tube Placement - Esophagostomy**

These tubes can generally be placed with a combination of a local anesthetic and sedation, or brief injectable anesthesia (such as ketamine-midazolam or propofol). The tube is measured to end in the distal esophagus as for the NE/NG tubes above and marked. Typically, a 10–14 French tube is used in cats and small dogs; larger tubes can be used in dogs. Carmalt forceps are advanced into the esophagus along the left side of the neck. Once past the angle of the jaw, the forceps are angled to tent the overlying skin and subcutis in the midcervical region. A small incision is made over the forceps and mosquito forceps used to bluntly dissect down to the Carmalts. The Carmalts are then used to grasp the distal end of the tube, and it is brought out through the mouth, leaving the flared end extending from the cervical incision. The oral end of the tube is then reversed and advanced down the esophagus normograde. The tube is now in its intended position and is secured to the skin with tape butterflies and suture. A light wrap can be placed over the tube stoma for the first few days, but care must be taken not to make the wrap too tight and cause respiratory distress. Feeding can commence immediately upon patient recovery.

**Tube Placement - Gastrostomy**

Gastrostomy tubes are always placed in anesthetized patients, and the easiest method of placement involves endoscopic assistance. (Percutaneous endoscopically placed gastrostomy or PEG tube). PEG tubes generally come in kits with all the necessary supplies, and they come in various sizes. The anesthetized patient is placed in right lateral recumbency, and an area on the left flank extending behind the last rib is clipped and a surgical scrub performed. The endoscope is advanced into the stomach, and the stomach is insufflated. A trocar or large-bore needle is advanced into the stomach and identified with the endoscope. A guideline (usually monofilament suture) is advanced through the needle and grasped with endoscopic instruments. The guideline is retracted from the stomach with the endoscope and attached to the tube, with care taken not to remove all of it from the patient. (Most tubes have a plastic cone-shaped adaptor on the end that facilitates exit from the stomach.) The guideline is now drawn back by pulling on the end exiting the abdomen, and the tube is thus advanced into the stomach. Once the line has been pulled such that the tube is flush with the mucosa, a small incision is made at the guideline exit site to allow the tube to exit. The tube is pulled out until the mushroom tip lodges it against the mucosa. The pressure of the mushroom tip keeps the serosa of the stomach against the peritoneum and helps prevent leakage.

A rubber flange (included in most PEG tube kits) is slid down the tube by inserting a hemostat through the slit in the flange, grasping the end of the tube, and withdrawing the hemostat. Slide the flange down until it contacts but does not create tension against the body wall. Attach a piece of tape to the tube about 2 cm above the skin (or use superglue) to prevent flange slippage. Suturing the tube to the skin is not necessary or recommended. Cap the tube with an intravenous catheter cap or 3-way stopcock.
Bandage material may be used if desired to protect the tube and keep the end of the tube in a convenient position for feeding. A "sweater" fashioned out of a stockinette makes a very convenient dressing, especially in cats. The tube stoma should be checked daily for discharge or erythema.

Feeding can start 12–24 hours after tube placement. Tube diameter is sufficient to accommodate feeding blenderized commercial canned foods made for hepatic disease. Flushing the tube with 5–10 ml of water should follow each feeding to prevent tube blockage.

**Tube Complications and Troubleshooting**

Tube dislodgement is a common complication for NE and NG tubes, and it can be avoided by securing the tube to the muzzle and using an Elizabethan collar. Esophagostomy tube dislodgement is uncommon, but it is not of great concern due to the healing capacity of the esophagus. Interruption of feeding or nil per os (NPO) is not necessary after esophagostomy tube dislodgement. On occasion a patient will vomit up an esophagostomy tube and chew off the segment protruding through the mouth. The remaining portion must then be removed from the stoma site.

Abscesses and cellulitis can sometimes form at tube stomas - culture and appropriate antibiotic therapy are usually sufficient, and tube removal is not indicated unless the patient is systemically ill or there is a risk of peritonitis.

Early PEG tube removal (before 14 days) increases the risk of peritonitis, and the patient should be closely monitored for signs of systemic illness and abdominal pain. The patient should be held NPO for 24 hours to reduce the risk of leakage.

Tube obstruction can be managed by attempting suction or flushing of the tube first. If that fails, a carbonated beverage, such as a soft drink, can be flushed into the tube under pressure while the injection port is occluded. The carbonation will expand and may push the obstruction into the gastric lumen.
Exotic Animal Practice Tips
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Belton Animal Clinic and Exotic Care Center, Belton, MO, USA

PRACTICE TIPS FOR REPTILES
- Place on substrates that are not easily ingested - no calcium-containing sand.
- Feed appropriately sized food and prey items.
- In iguanas and some of the other lizards, recommend spaying/neutering prior to sexual maturity.
- Discuss long-term problems of keeping reproductively intact.
- Do not aggressively palpate females with distended coeloms or over-restrain for procedures (preovulatory stasis, egg bound, egg yolk peritonitis).
- Kidney disease prevalent in adult iguanas probably due to chronic dehydration and high protein diets when they were young.
- Encourage feeding of dead prey - fresh killed/frozen.
- Live prey should be removed if not eaten within five minutes.
- Tail amputation done manually at natural breaking planes. Do not suture.
- Snakes that are pre-shed will have a rosy “glow” to the ventrum, which is different than the petechial hemorrhages that are seen with snakes with septicemia.
- Warn clients of possible long-term complications and dysfunction from early severe NSHP.
- Ivermectin - not in turtles, tortoises, and indigo snakes; with caution in skinks; not within 10 days of ketamine use.
- Standing lateral view allows for better visualization of air space, better definition of ileus and more information in lizards.
- Careful what you say! **Never assume.**
  - “Keep warm during transport.”
  - “Swim once per day.” - Specific swimming recommendations
  - “Give this once per day.” - Specific recommendations on dosing
  - “Increase the temperature of the cage.” - Specific recommendations on heat changes
- Thermal burns are common, as heat receptors are not the same as pain receptors and will seek heat especially if ill.
- No Ice fluids with space-occupying lesion.
- At least annual PE, biannual fecal exams.
- Not all “Reptile Lights” are the same.
- Define “gut loading” insect prey items.
- Discuss *Salmonella* risks with all clients.
- Brochure on *Salmonella* and Reptiles available through ARAV.
- **ANY disease process or procedure that is considered painful in other species should be considered painful in reptiles!**

PRACTICE TIPS FOR SMALL MAMMALS
- It is safer to place a rabbit backwards into a cage to prevent injury from kicking as you place it in.
- Keep head elevated and neck un-crimped when rabbits and guinea pigs are anesthetized.
- Do not tie legs; gently tape them out of your field.
- Non-herbivorous small mammals should have only limited fasting - four hours or less - prior to surgery.
- Rabbits and guinea pigs should not be fasted for surgery. Swab mouths after induction.
- Check for subgingival spurs of the 1st upper PM in chinchilla that is interested in food but not eating.
Guinea pigs will readily walk off the edge of the table so should always be carefully monitored.

Obesity is an increasing problem in exotics, and clients should be counseled early about nutrition and exercise. Signs associated with obesity: difficulty grooming (especially perianal area), posturing difficulty for urinating and defecating (urine scald, dirty feet and legs), difficulty posturing for normal functioning.

Always provide a towel for traction on the exam table.

Provide food items **after** oral exam.

Hedgehogs, hamsters and other small mammals - can be difficult to examine their ventrum awake: place in clear plastic container to see ventrum.

Dental procedures in small mammals should not be performed without proper speculums.

Never pull tongue outside of mouth.

Don’t forget that other small mammals need dental care too: ferrets, coatimundi, pot-bellied pigs, etc.

Never lift rabbits and guinea pigs up by the scruff or pick rabbits up by the ears.

Keeping patients warm during surgery is important, but it is easy to overheat small mammals that are not carefully monitored.

Rabbits and ferrets should never be declawed.

Alopecia of the lateral abdomen or flanks can indicate pain; can be due to hormonal changes.

The risk of anesthesia is much less than the risk of reproductive problems in rabbits.

Consider the same for guinea pigs and rats.

Examine the penis of male guinea pigs to check for hair and sebaceous secretions that may build up.

Never shave the bottom of the hind feet of rabbits.

Perivascular necrosis can occur with extravasation of injectable drugs in the marginal ear vein of rabbits.

Analgesics are imperative in sugar gliders before, during and after surgery, as they have a tendency to self-mutilate areas of pain/irritation. Distract with preferred food items as they wake up.

Use food items to distract small mammals, such as hedgehogs and sugar gliders, during the examination.

**Practice Tips for Exotics**

- Create a hospitalization ward for exotics away from other pets, and rooms with ability to change temp and humidity for reptiles and birds.
- Keep fish wet with the water they arrived in and place them often back into the water between procedures; wear exam gloves and wet them as well.
- Venipuncture in fish can be done with fish anesth. or awake and taken from just ventral to the lateral line on the tail.
- Instruct clients to bring in 2 large pails of tank or pond water that the fish is used to in order to facilitate anesthesia.
- **Analgesics should be provided immediately if pain is detected, before** diagnostic procedures and treatment are pursued.
Handling and Restraint and Venipuncture of Exotic Animals

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**Basic Reptile Handling and Restraint**
- Know the natural defense mechanisms of each species
- Train staff members appropriately
- Define roles prior to handling
- Gather supplies prior to handling

**Lizards**
- Tail whipping
- Biting
- Nails
- Your defense: Control serpentine movement and control tail
- Many lizards have the ability to “drop” their tails if restrained by the distal aspect
- Be careful not to lean against the tail and trap it against the table as you restrain it

**Snakes**
- Teeth
- Constriction
- Tail
- Defecation/urination/musk glands
- Your defense: Support the snake well, hold head gently but firmly, and move as the snake moves; “Act like a tree”- a snake that is well supported is less likely to resist or get injured during handling and will be less stressed
- Locate head
- Pin the head
- Place tail first in container

**Turtles**
- Nails
- Beak
- Legs
- Spurs and pointed shells
- Urine
- Your defense: Hold midway between front and rear legs
- Sedation/anesthesia may be necessary for larger patients

**Amphibians**
- Nets, plastic containers
- Restrain heads of hellbenders, large toads and giant salamanders
- Minimize handling
- Moisten exam gloves
- Moisten paper towel/dishcloth

**Basic Ferret Handling and Restraint**
- Most ferrets are easy to handle, but a new ferret must be approached slowly until this can be verified.
- Allow ferret to approach you.
- Distract the ferret with one hand and then pick it up with the other hand by gently grasping it around the middle.
- If the ferret attempts to bite, keep it in motion.
- The scruff can be grasped if necessary - grab as deeply as you can from both sides of the neck.
- Distract it with your other hand or by blowing in its face.
- When a ferret bites, it will usually not let go easily, and if the “victim” struggles, it will bite harder.
- You may have to wait for them to let go.
- Placing them down on the table or floor, blowing in their face, or spraying them with water may get them to release.
- Sleeping ferrets should be awakened before they are picked up.
- Scruffing them and allowing them to hang from the scruff virtually immobilizes them like a cat with a kitten.
- Sometimes the head needs to be pressed against the table to scruff them safely.
- Provide favored food items to facilitate exams.

**Basic Hamster/Gerbil Handling and Restraint**
- Hamsters and gerbils should also be allowed to become fully awake before handling.
- They may be able to be scooped up by hand or in a container.
- They can be scruffed if necessary, although this may be difficult to do and is not quite immobilizing like a cat with the kitten.
- Gerbils can also be lifted by the base of the tail.
- If lifted or restrained by the tip of the tail, the skin of the tail will come off.
- Provide favored food items to facilitate exams.

**Basic Rat/Mouse Handling and Restraint**
- Approach slowly.
- Allow to wake up if sleeping.
- It often helps to catch them in a container such as a coffee can or cardboard tube.
- Mice can be restrained by the base of the tail.
- Restraining by the tail away from the base will cause degloving of the skin to occur.
- Rats can be restrained by the scruff but rarely need to be.
- Most rats, when handled gently, are easily handled.
- Provide favored food items to facilitate exams.

**Basic Sugar Glider Handling and Restraint**
- As a nocturnal species, they are best handled at night or in dimmer light
- Can be scruffed
- Will “gritch” when wakened
- Should be well supported when held
- May jump or glide away and can be fast
- Provide favored food items to facilitate exams and recovery from anesthesia/surgery

**Basic Chinchilla Handling and Restraint**
- Are normally gentle but not always used to being handled
- Can bite if really frightened
- Will experience “fur slip” when restrained
- Grasp gently but firmly by the base of the tail
- Provide favored food items to facilitate exams
**BASIC GUINEA PIG HANDLING AND RESTRAINT**
- Talk to them quietly as you handle them
- Scoop them up by placing one hand behind the front legs and one hand supporting the rump and rear legs
- Will readily walk off a table
- Do best in pairs or trios but will fight if not bonded slowly

**BASIC RABBIT HANDLING AND RESTRAINT**
- Talk to them quietly as you handle them
- Scoop them up by placing one hand behind the front legs and one hand supporting the rump and rear legs
- Hold under your arm like a football if frightened
- Cover eyes if necessary
- Can break their own back if they kick when not well restrained
- **Can break their backs and legs when jumping from your arms**
- Can break their own backs when you place them in the cage as they jump in and kick back; therefore, place in backwards

**BASIC AVIAN HANDLING AND RESTRAINT**
- Minimize handling
- Have everything ready before you handle
- Need breast muscles to breathe, so do not constrict
- Hand towel or paper towel
- Dim lights and create spot light
- Hold head between thumb and first finger, then wrap fingers around wings
  - Can hold around “cheeks”
  - Can hold around top of head and below beak

**ZOONOTIC POTENTIAL OF EXOTIC ANIMALS AND WILDLIFE**
- Ringworm
- Bacteria
- Fungi/dermatophytes
- *Salmonella* sp.
- Parasites
- *Baylisascaris, Giardia, roundworms, hookworms*

Keep in mind the size of your patient when determining what procedures you will perform and what treatments you will choose.

Keep in mind the level of patient compromise when determining procedure and treatment to be performed.

**CARE TIPS FOR EXOTIC ANIMALS**
- Know basic environmental needs
- Temperature
- Temperature gradient
- Humidity
Be prepared to stimulate the appropriate environment for each species when patients are hospitalized, boarded or impounded
Rabbits and guinea pigs overheat readily
If kept outside, provide shade and ventilation
If not sure, provide a hidebox
Know whether the species is carnivore, herbivore or omnivore
Feed appropriately sized prey
Prefer dead prey
Never keep live prey in longer than 5–10 minutes

**Venipuncture of Reptiles**
- **Snakes** - Tail vein, cardiocentesis, jugular
- **Turtles** - Jugular, anterior brachial vein, tail vein
- **Lizards** - Jugular, tail vein, ventral abdominal vein

**Venipuncture of Small Mammals**
Anesthesia is recommended for all but rabbits and ferrets.
- **Ferrets** - cranial vena cava, jugular, saphenous vein, cephalic vein
- **Hamsters/gerbils** - cranial vena cava, orbital sinus bleed (?)
- **Rats/mice** - cranial vena cava, ventral tail vein/artery
- **Sugar Gliders** - cranial vena cava, saphenous vein, femoral vein
- **Chinchillas** - cranial vena cava, cephalic vein, saphenous vein
- **Guinea pigs** - cranial vena cava, jugular, cephalic vein, saphenous vein
- **Rabbits** - lateral saphenous vein, cephalic vein, jugular vein

**Venipuncture of Birds**
Right jugular vein, brachial vein, tarsometatarsal vein
Recognizing Signs of Pain and Pain Management in Exotics
Teresa Bradley Bays, DVM, CVA, DABVP (ECM)
Belton Animal Clinic and Exotic Care Center, Belton, MO, USA

**Physiologic “Stress” Response to Pain**
- Vasoconstriction
- Increased heart rate and stroke volume
- Decreased GI and urinary tone
- Endocrine responses
- Nociceptive stimulation of brain
- Enhance reflex sympathetic responses
- Immune suppression
- Impaired wound healing
- Decreased food and water intake
- Secondary medical problems
- Gastric ulcers, GI stasis
- Shock, death
  - Higher rate of anesthetic death in exotics?
  - Higher rate of death postoperatively?

How is this related to inadequate use of pre-, intra-, and postoperative analgesics in prey species?

**Behaviors Associated with Pain in Small Mammals**
- Predators such as ferrets are more likely to show overt signs of pain
- Prey species such as rabbits and guinea pigs are less likely to show overt signs of pain
- Half-closed/dull/unfocused eyes
- Aggressive when normally docile
- Pressing abdomen on the floor
- Immobility/lethargy/isolation
- Fewer, smaller or no fecal pellets
- Vocalization (squeal may be fear in rabbits)
- Teeth grinding (bruxism)
- Reluctance to curl when sleeping (ferrets)
- Stretching with back arched
- Tucked appearance
- Strained facial expression with bulging eyes
- Lameness/ataxia
- Polyuria/polydipsia (especially with GI pain)
- Anorexia
- Stiff movements
- Increased frequency and depth of respirations or rapid, shallow breathing
- Head extended and elevated
- Stinting on palpation
- Porphyrin secretion (stress)
- Self-mutilation
- Squinting (especially ferrets)
- Piloerection
• Chewing at affected site
• Hunched posture

**Behaviors Associated with Pain in Birds**
• Unable to rest/reluctance to perch
• Frequent shifting postures
• Crouch-like stance with head pulled in to body
• Over-grooming/lack of grooming
• Feather picking, biting or scratching affected area
• Aggression in normally passive animal
• Striking out to avoid being handled
• Ruffled feathers
• Increased respiration/mouth breathing
• Lameness/ataxia/wing droop
• Vocalization/withdrawal
• Guarding behavior
• Immobility/lethargy/isolation
• Flight response
• Closed eyes
• Rigid stance
• Anorexia
• Rolling or thrashing
• Splinting of the abdomen
• Absence of normal behaviors

**Behaviors Associated with Pain in Reptiles**

**Lizards**
• Anorexia
• Hunched posture, remain standing
• Scratching or flicking foot at affected area
• Aggression in normally passive animal
• Stinting on palpation
• Flight response/startle easily
• Closed eyes
• Aerophagia/dilated esophagus/dysphagia
• Head elevated and extended
• Color changes
• Avoidance/withdrawal
• Biting at affected area
• Immobility/lethargy/lameness/ataxia
• Absence of normal behaviors
• Rapid respiration

**Snakes**
• Hold body less coiled at site of pain
• Tucked up and writhing in affected area
• Restless/agitated
• Easily startled
• Absence of normal behaviors
- **Chelonians**
  - Intermittently pulling head into shell and then extending the neck out and up

- **Amphibians**
  - Flick foot or bite at affected area
  - Color changes
  - Rapid respiration
  - Absence of normal behavior

### PAINFUL DISEASE PROCESSES
- Trauma
- Gout
- Peritonitis
- Pancreatitis
- Pneumonia
- Abscesses
- Frostbite
- Post surgery
- Hepatitis
- Burn wounds
- Cystitis
- Osteoarthritis
- Mastitis
- Gastrointestinal stasis
- Urethral obstruction
- Visceral pain
- Meningitis
- Limb amputation
- Severe dermatitis
- Cancer pain
- Prostatic abscesses
- Stomatitis
- Enteritis
- Intestinal foreign body
- Dental disease
- Gastric torsion
- Dystocia
- Ophthalmic disease
- Pododermatitis

### PAIN MANAGEMENT CONSIDERATIONS
- Preemptive analgesia
- Neuropathic pain
- Inflammatory pain
- Decreases dose of maintenance anesthetic
- Care with injectable anesthetics
- Individualize treatment and provide multimodal pain therapy
- Numerous pain pathways
- Synergistic effect
Analgesics often used at lower doses
- Anxiety lowers the pain threshold
- The effects of illness, restraint and environmental changes with hospitalization increase the level of stress experienced
- Never discount the owner’s concern - familiarity with daily behavior is important in assessing pain
- Train your staff to recognize pain in exotics
- Assign staff member to monitor patient throughout hospitalization

**NSAIDs**
- Don’t use with renal and hepatic impairment, bleeding disorders, enteritis, gastritis, gastric ulcers, hypotension or hypovolemia
- Don’t combine with corticosteroids
- Use lower doses with ferrets
- Use with caution for prolonged use in herbivores; use gastric protectants
- In birds, Banamine may cause regurgitation and tenesmus, blood in stool and renal damage at higher doses/prolonged use

Hypotension is often seen as an anesthetic complication in small mammals - use pre-op NSAIDs with caution.

**Opioids**
- Avoid use in hypotensive patients
- Short duration of action
- Decrease need for isoflurane
- Administer during lighter plane when also using injectable anesthesia
- Butorphanol - least potent and shortest duration
- Buprenorphine - intermediate strength and longest duration (6–8 hrs)
- Morphine - most potent and intermediate duration
  - Oral buprenorphine (transmucosal) has been found pharmacologically effective in cats and more recently in dogs (abstract from ACVA mtg); clinically effective in rabbits and ferrets
  - Pica has been noted in rats on buprenorphine
- Ferrets can be prone to side effects including hypotension, sedation and respiratory depression
- Guinea pigs, rabbits, and chinchillas can be prone to side effects associated with the GI tract

**ANALGESIC DOSAGES**
Please consult exotic animal formularies for specifics on each species concerning indications, contraindications, pharmacokinetic data, comments and accurate dosing. The dosages listed here have been used successfully by practitioners; however, careful consideration must be made on an individual basis for each patient as to what dose and what analgesic are best for that particular case. This author uses some of these analgesics at the lower end of the dosages given and has great success using multimodal therapy.

**ANALGESICS FOR SMALL MAMMALS**

**NSAIDs**
- Acetylsalicylic acid - 10 to 100 mg/kg q 8–24 h PO
- Carprofen - 1 to 4 mg/kg q 12 to 24 h PO, SQ, IM
- Flunixin meglumine - 0.1 to 2 mg/kg q 12–24 h SQ, IV, IM (herbivores)
- Piroxicam - 0.2 mg/kg PO q 8 h
- Ibuprofen - 2 to 7.5 mg/kg q 4 to 24 h IM, PO
- Ketoprofen - 1 to 3 mg/kg IM, SQ, PO q 24 h
- Meloxicam - 0.1 to 1.5 mg/kg q 24 h SQ, PO (Safety studies have not been done for higher dosages)
  - Meloxicam (Metacam)
    - 6 to 8 h to reach blood levels, so use well before procedure for post-op pain
    - Possibly due to rapid metabolism, higher doses may be needed in rabbits/rodents
      - 0.3 mg/kg/day PO in rabbits (Turner, et al.)
      - 1–2 mg/kg pre-op in rats (to achieve post-op pain) (Roughan and Flecknell)
    - Ferrets can be more sensitive to NSAID side effects, so be more cautious with dose (similar to cats)
    - Do not use in ferrets if ulcers are suspected or if vomiting/diarrhea or melena is present
    - Blood work to R/O liver/kidney disease

Opioids
- Butorphanol - 0.1 to 0.5 mg/kg q 4–6 h SQ, IV, IM
- Buprenorphine - 0.01 to 0.1 mg/kg q 6 to 12 h SQ, IM, IV
- Tramadol (syn. Analogue of codeine) 4.0 to 11.0 mg/kg q 12–24 h PO
  - Pharmacological studies indicated 10 mg/kg safe in rabbits (TBB uses 3 mg/kg)
  - Can decrease blood glucose levels
- Morphine - 1.25 to 5 mg/kg q 2–4 h SQ, IM
- Oxymorphone 0.05 to 0.2 mg/kg q 4–12 h SQ, IM
- Meperidine 5–10 mg/kg q 2–4 h IM, IV, SQ
- Hydromorphone 0.05 to 0.2 mg/kg q 6 to 8 h IM, SQ
- Fentanyl
  - 0.0074 mg/kg IV
  - 0.15 to 0.44 ml/kg IM (can cause muscle necrosis)
  - Fentanyl citrate 10–30 microgram/kg/h via CRI
  - Fentanyl patches - Rabbits: 1/3 to 1/2 patch/3 kg rabbit X 3 days (do not cut patch; cover unused portion instead)

Combining NSAIDs and opioids provides multimodal analgesia (usually at lower dosages) with less side effects.

Miscellaneous
- Gabapentin 3–5 mg/kg q 8–24 h PO (anticonvulsant used for neurogenic pain)

Local Analgesia
- Lidocaine at incision site 2% 1 mg/kg - can be used in combination with bupivacaine for longer analgesia
- Bupivacaine 0.5% 1.0 mg/kg - slower onset but can be used in combination with lidocaine for longer-duration analgesia
- Cetacaine on wounds from maggots and on incisions if chewing postoperatively

Epidural Analgesia
- Lidocaine 1.5% 0.4 ml/kg
ANALGESICS FOR BIRDS

Local
- Lidocaine 1 to 3 mg/kg SQ
- Bupivacaine 2 to 10 mg/kg SQ

NSAIDs
- Acetylsalicylic acid - 5 mg/kg q 8 h PO
- Carprofen - 1 to 4 mg/kg IM, IV, PO
- Flunixin meglumine - 1 to 10 mg/kg q 12–24 h IV, IM
- Ketoprofen - 1 to 4 mg/kg IM q 12–24 h
- Meloxicam - 0.1 to 0.5 mg/kg q 12–24 h IM, PO

Opioids
- Buprenorphine HCl - 0.05 to 1.0 mg/kg q 12 h IM, IV, SQ
- Butorphanol tartrate - 0.5 to 5 mg/kg q 4 h IM, IV, SQ
- Morphine sulfate - 1 to 3 mg/kg q 4 h IM, SQ
- Fentanyl citrate - 0.2 to 2 mg/kg IM, IV, SQ (not very effective, can cause hyperactivity in 15–30 minutes)

Miscellaneous
- Gabapentin 3 to 11 mg/kg q 12–24 h PO (anticonvulsant used for neurogenic pain)

ANALGESICS FOR REPTILES AND AMPHIBIANS

Local
- Lidocaine 2 to 5 mg/kg SQ
- Bupivacaine 1 to 2 mg/kg SQ

NSAIDs
- Carprofen - 1 to 4 mg/kg q 24–72 h IV, IM, PO, SQ
- Flunixin meglumine - 0.1 to 1 mg/kg q 12–24 h IV, IM
- Ketoprofen - 2 mg/kg q 24–48 h IM, SQ
- Meloxicam - 0.1 to 0.5 mg/kg q 24 h PO

Opioids
- Buprenorphine HCl - 0.01 to 1.0 mg/kg q 12–24 h IM
- Butorphanol tartrate - 0.05 to 1 mg/kg q 12 h IM, IV, PO, SQ (up to 20 mg/kg in tortoises)
- Morphine - 0.5 to 4.0 mg/kg IM, Ice
- Fentanyl - 2.5 mcg/h patch to caudodorsal lumbar region (environmental temperature may affect absorption)
- Oxymorphone 0.025 to 1.5 mg/kg q 12–48 h IM, IV, SQ
- Tramadol 5.0 to 10.0 mg/kg q 24 h PO

ALTERNATIVE APPROACHES TO PAIN MANAGEMENT
- Acupuncture
- Massage therapy
- Chiropractic
- Physiotherapy
- Cranioelectrical stimulation (CES)
  - Alpha Stim™
  - Uses a biphasic square electrical wave
- Rx for pain, anxiety, depression and insomnia
- Current studies in amputees and breast cancer patients
- Pain, wound healing, anxiety in animals
- Produces the alpha state within the body’s electrical activity pattern
- Calmness, mental focus, pain control
- Dysregulation of firing patterns in the brain responsible for behavioral anomalies: depression, anxiety, insomnia, addictions, OCD, etc.
  - Microcurrent electrical therapy (MET)
    - Electrical current stimulates healing and growth and regeneration
    - Initiates and sustains chemical and electrical relations in the healing process
    - Bacteria do not like the microcurrent
    - Injury causes a change in polarity that is reestablished with MET

**Assessment of Response to Analgesics**
- Return to normal behavior
  - Eating
  - Sleeping
  - Stretching
  - Grooming

**Other Considerations**
Always sedate or preferably anesthetize small mammals and birds before euthanasia.
Stress and the Single Guinea Pig
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- In domestic animals, wellbeing is defined as the absence of stress.
- Stress is, however, difficult to measure and perceive objectively in nonverbal species such as exotics.
- There is no specific biological measurement of stress - cortisol, for instance, can be high with stress, activity, and/or excitement.
- Much variability among individuals in how they respond to the same stressors.
- Guinea pigs exhibit increased cortisol levels when separated
  - Social stress early in pups
  - Stress in pregnancy
  - Less stress indicators in presence of females, known or unknown

What do exotics perceive as stressful?
- Physical restraint
- Fear of predators
  - Perceived vs. real
- Overheating
- Travel
- Lack of food
- Lack of water
- Overcrowding
- Changes in routine
- Excessive noise/movement
- Social species - lack of social contact
  - Guinea pigs, rabbits, sugar gliders, etc.
  - Hand-raised birds, which have not developed independent behavior, away from their “human”
- Nonsocial species - exposure to others
  - Male Beta fish
- Excessive interaction
- Not enough interaction
- Forced confinement
- Territorial aggression

How does stress affect exotic pets/patients? - Clinically
- Stereotypic behaviors: repetitive behaviors with no obvious function
  - Pacing/repetitive route tracing
  - Continuous somersaults in birds
  - Continuous head bobbing
  - Grooming to excess
  - Repetitive pecking at the same spot
- Depression/lethargy
- Fear
- Restlessness/excitability
- Diarrhea
- Social withdrawal
- Aggression
- Pica
- Color changes in reptiles
- Decreased body weight
- Weight loss despite food consumption
- Cannibalism
- Abandonment of young
- Over-grooming: disperse tension or stress/dissociative behavior
- Self-mutilation
- Feather-picking
- Overeating: acute stress
- Anorexia: chronic stress
- Stress bars in bird’s feathers

**HOW DOES STRESS AFFECT EXOTIC PETS/PATIENTS? - PHYSIOLOGICALLY**
- Increased cortisol levels
- Increased catecholamine release
- Increased incidence of ulcers
- Decreased immune response
- Elevated blood pressure
- Elevated heart rate: acute stress
- Bradycardia: chronic stress
- Renal ischemia
- Decreased body temperature
- Increased respiratory rate

*All of these things interfere with recovery from surgery and illness!*

**STEPS TO TAKE TO DECREASE STRESS IN EXOTICS**
- Light cycles appropriate for that species
  - Nocturnal vs. diurnal
- Provide enough space for the species housed
- Provide visual barriers
  - Hideboxes
  - Huts, igloos, towels
  - Plantings, foliage
- Create opportunities for foraging/puzzle feeders
- Provide scratching posts
- Provide climbing frames
- Provide nest boxes and nesting material for those you wish to be reproductively active
- Provide appropriate elimination areas or litter pans
- Provide showers/wallows if appropriate
- Provide novel objects to the environment to increase spatial memory and decrease stress to new situations
- Provide shelters, platforms, heat and light and temperature gradients for thermal regulation
- UVB exposure if maintained indoors
- Opportunities and space to exercise
- Opportunities for sensory stimulation
- Opportunities to hide/escape

**Steps to Take to Decrease Stress in the Clinic**
- Postpone medical procedures if stressed/painful
- Minimize handling
- Allow animal some control over its environment
- Provide toys and items of enrichment
- Provide proper temps/humidity/UVB
- Ability to change spaces to provide for different sizes/environmental needs
- Don’t transport or house in high traffic areas and house species separately
- Cover eyes of patient if stressed
- Anesthetize for procedures if easily stressed
- Handle only once in severely stressed patients
- Prepare ahead for all scenarios
- Provide a towel or mat on the exam table for traction
- Provide hay and greens for herbivores after the teeth are checked
- Consider allowing bonded mates to be housed together when admitted for Sx, boarding and hospitalization
- Provide them with familiar objects from home
- Return them to the home as soon as possible
- Remember that with prey species, the DVM and staff may be perceived as predators
- Speak softly
- Move slowly and deliberately
- Don’t overwhelm patient
- Dim lights if appropriate
- **Pain management!**

**Advice for Clients with Exotic Pets**
- Acclimate pets to the travel cage so they are less afraid when a vet visit is needed
- Do not put new pets into enclosure with established pets
  - Same species
  - Other species
- House different species separately
- Provide housing that does not allow for reflection to be seen in species that are territorial/solitary
- Provide environmental and behavioral enrichment

**Signs of Decreased Stress**
- More play behaviors
- Increased weight gain without increase in food consumption
- Decreased aggressive behaviors
- Less feather-picking
- More foraging behaviors
- Appropriate grooming and mutual grooming
- Presence of normal behaviors
Understanding & Managing Rabbit Behavior Problems

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- Understand normal behavior
- Know subtle behavior changes that indicate problems
- Educate clients early to monitor for these behavioral changes

**HEALTHY RABBITS - UNDERSTANDING NORMAL BEHAVIOR**

- Inquisitive
- Alert and curious
- Bright eyes
- Will often eat if offered favored treats
- Timid in strange surroundings, but eyes are bright and postures normal
- Will “shake off,” groom, investigate and eat as becomes more calm
- May lay out with rear legs stretched

**UNHEALTHY RABBITS**

- Lifeless, glazed and unfocused eyes
- Immobile, stop grooming
- Lack curiosity about their surroundings
- Isolation from bonded mates

**SENSORY BEHAVIORS**

- Vision - Laterally placed eyes
  - Scanning
- Tactile: Lips and vibrissae
  - Startle if hand placed beneath their noses
- Hearing
  - Sensitive to loud noises
  - Thermoregulation
- Olfactory
  - Scent glands
  - Fecal pellets/anal gland secretions
  - Latrine sites
  - Scent of kits

**REPRODUCTIVE BEHAVIORS**

- Sexual maturity is function of size, not age
  - Small breeds - 4–5 months of age
  - Medium breeds - 4–6 months of age
  - Large breeds - 5–8 months of age
- Male rabbits
  - Courtship - Chinning, enurination, muzzle, groom, tail flagging
  - Mating - Bites the female at nape of neck, ejaculation soon after intromission, male then falls on his back or his side and lets out a sharp cry
- Female rabbits
  - Induced ovulators
Receptive females exhibit restlessness, lordosis, chinning, congested vulva.
Non-receptive females will run away, bite, vocalize.
Stress due to crowding, disease and predators may cause resorption of embryos at midterm.
Nesting is evident and occurs 1–2 days prepartum.

Neutering decreases urine and fecal marking.
Spaying decreases reproductive neoplasia and hormonal behaviors.
False pregnancy common.
Keep separated for at least 30 days after altering.

**COMMUNICATION BEHAVIORS - RABBITS**
- Grunt, growl, snort, barking - anger/annoyance/territory protection
- Honking/oinking - for food/attention/courtship
- High-pitched, repetitive scream - fear/terror/pain
- Fear - motionless, crouched position with feet beneath body, head extended, ears flattened against head, eyes bulging
- Alert - ears forward or held laterally
- Erect tail - excitement/anticipation/if threatened
- Tail twitching - courting/urine spraying
- Presenting - flat on floor with feet tucked/head extended/chin on floor (submissive)
- Licking - sign of affection
- Nipping - anger/seeking attention
- Tooth purring - low-pitched hum with teeth lightly vibrating and whiskers quivering
- Teeth grinding - slower, louder tooth crunching with bulging eyes due to pain
- Wheezing, sniffing - talking/irritation
- Chinning - mark with secretions from chin (geographical differences in components, maintains dominance hierarchies)
- Urine spraying

**SOCIAl BEHAVIORS IN RABBITS**
- Social species
- Increased cortisol levels if separated
- Increased exercise and interaction
- Safety in numbers
- Bonding should be supervised

**GROOMING BEHAVIORS - RABBITS**
- Meticulous groomers
- Clean ears with rear feet
- Mutual grooming
- Grooming after handling
- Do not bathe
- Longhaired rabbits
- Ectoparasites - seborrhea, alopecia, pruritus, aural discharge

**LACK OF GROOMING**
- Obesity
- Arthritis or other pain
- Discospondylosis
- Orofacial pathology
- Intense pruritus/parasites
- Lethargy (insulinoma in ferrets)
- Diarrhea/fecal matting

**EATING BEHAVIORS**
- Herbivorous - need high fiber/low protein
- No sugars or starches
- Lateral/circular grinding motion of jaw
- Develop food preferences early
- Any change in eating habits significant
- Lack of food - polydipsia, lack of water - anorexia
- Counsel owners about how food and water are provided and maintained
- Water bowl may prevent chronic dehydration

**OROFACIAL PATHOLOGY**
- Subtle signs: Pick up/interest in food but then drop it, change food preferences, dull/quiet
- Obvious signs: Hypersalivation, pawing at the mouth, anorexia, lack of grooming, swelling and pain on palpation of affected area
- Examine teeth with otoscope at every exam
- Anesthesia and use of proper speculums are mandatory for complete exam, trimming and filing teeth - do not pull the tongue outside of the mouth

**ELIMINATION BEHAVIORS - RABBITS**
- Defecation
  - Relatively passive process, sitting position, tail down
  - Continuous throughout the day
  - Rarely constipated
- Cecotropes
  - Overproduced with diets high in proteins
  - Obesity impairs grooming
  - Grass hays, decreased or no pellets, increase activity

**URINARY BEHAVIORS - RABBITS**
- Micturition is a relatively passive process and tail is only lifted slightly
- Straining will be evidenced by an exaggerated lifting of the tail and the hind end during micturition +/- vocalizations

**LOCOMOTOR BEHAVIORS/ACTIVITY**
- Normal ambulation - rabbits
  - Hop with rear legs simultaneously
  - Entire plantar surface of foot is used
  - Moving slowly only toes of rear feet touch the ground
  - When sitting, the entire plantar surface from hock to toes is in contact with the ground
  - Weight carried evenly on all 4 feet
- Subtle changes in ambulation and posture should be addressed
  - Walking vs. hopping with rear legs
- Sitting unevenly
- Leaning with one limb held close to the body
  - Active in morning and evening
  - Sleep or rest midday
    - Lay on sides or sternally with feet stretched out behind them
    - Often sleep with eyes open/startle
  - Like to perch
  - Like hideboxes (denning)

**CONTINUOUSLY CAGED**
- Obesity
- Pododermatitis
- Osteoporosis
- Behavioral problems
  - Exhibit more nervous behaviors
  - Repetitive behaviors
  - Over-grooming

**HOW DOES BEHAVIOR RELATE TO HOSPITALIZATION?**
- Towel for traction
- Hay and greens in exam room
- Not touching the nose during examination
- Prey species - separate from predators
- Provide hideboxes
- What foods and how is water supplied?

**OBESEITY**
- Too much food
- Too little exercise
- Associated medical problems
  - Difficulty grooming
  - Difficulty ambulating
  - Pressure on GIT, diaphragm
  - Pododermatitis

**PAIN**
- Know clinical signs of pain
- Address pain **before** diagnostics and other treatments
- Secondary physiological changes include gastric ulcers, decreased peripheral circulation, decreased temperature, GI stasis, and even death

**MANAGING BEHAVIOR PROBLEMS**
- Undesirables include urine and fecal marking, chewing, digging, and aggression
- Most obvious at 3 1/2 to 6 mos.
- Test boundaries, instinctive behaviors and more assertive
- Establishing social order in their “community”
- Usually temporary unless mishandled or not addressed at all
- Previous traumatic/painful events (including medical problems)
- Not meant to be “spiteful”
- Unrealistic expectations - not all rabbits react the same
- Unique personalities
- Avoid inadvertently reinforced negative behaviors - interacting less
- Control environment to eliminate negative behaviors
- Spay/neuter early
- Decrease confinement/increase exercise
- Decrease stress/anxiety
- Provide consistent schedule, including feeding and day/night cycle
- Distract to positive behaviors and then reward
- Divert attention to acceptable behaviors - digging box
- Rule out medical issues with twice-yearly exams
- Provide free-choice grass hays and high-fiber diet
- Eliminate rough handling
- Allow for foraging behaviors by hiding food and treats for them to find
- Provide interactive items that stimulate instinctive behaviors/decrease boredom
- Provide behavioral enrichment to stimulate them mentally

**Behavioral Enrichment**
- Simulate natural environment and counsel clients on how to best provide for their pets’ emotional and psychosocial needs
- Allow for play - Bonded pairs/trios
- Provide UVB lighting
- Cardboard boxes, PVC tubes
- Straw mats and baskets, low ramps
- Telephone books, paper cups
- Rabbit-safe toys, paper bags
- Toilet paper/paper towel tubes
- Dryer hose, empty paper bags

**Mourning the Death of a Bonded Mate**
- Eat less, lethargic, polydipsic
- Isolate themselves or may seek an increasing amount of attention
- Engage in misbehavior - chewing, digging
- How you may help:
  - Provide more attention, watch that they are eating and defecating
  - Allow them to “view” the dead mate’s body
  - Provide new mate ASAP - keeping in mind the difficulties of bonding new rabbits

**Behavioral Training Techniques**
- Clicker training
- Targeting
- Desensitization and counterconditioning
  - Get used to the stimulus at gradually increasing levels
  - Associate the stimulus with positive reward so a positive emotional response is gained
Ferret Behavior & Enrichment
Teresa Bradley Bays, DVM, CVA, DABVP (ECM)
Belton Animal Clinic and Exotic Care Center, Belton, MO, USA

BEHAVIOR OF FERRETS

Healthy Ferrets
- Inquisitive
- Alert and curious
- Bright eyes
- Will often eat if offered favored treats
- Ferrets will chew, dig, and investigate
- Ferrets are either in constant motion or sleeping

Unhealthy Ferrets
- Lifeless, glazed and unfocused eyes
- Immobile, stop grooming
- Lack curiosity about their surroundings
- Isolation from bonded mates

Sensory Behaviors - Ferrets
- Vision
  - Binocular vision, turn head to see
  - Good vision in low light, not in the dark; difficulty adjusting to bright light
- Hearing
  - Ear canals open after 32 days
  - Respond to high-frequency sounds (squeaky toys)
- Olfactory
  - 60–90 days imprinting; will not eat any other prey
  - Offer variety of food in 1st 6 months
  - Keen sense of smell

Reproductive Behaviors - Ferrets
- Sexual maturity at 8–12 months of age
- Increased sexual activity longer light
- Males (Hobs)
  - Increased neck biting and pelvic thrusting behavior in play
  - Increased scent gland marking
  - Intromission 30 minutes to 3 hours
- Females (Jills)
  - Little estrus-associated behavioral changes - more excitable and nervous, sleep less, and eat less
  - Swollen vulva, flaccid/submissive when ready to breed
  - Remains in estrus until bred, OVH or medical intervention - severe anemia due to hyperestrinism

Communication Behaviors - Ferrets
- Anal drag, wiping, body rubbing
  - Provides info on sex and hormonal activity
- Back up and defecate in a corner
Ferrets: Bark - loud chirp of fear or excitement
Hiss - fear, anger, frustration, warning
Greet new ferret by sniffing anal, neck and shoulder area
Scream - high-pitched screech depicting fear or pain, during seizures
Dook, chuckling, buck - series of chortles depicting excitement, happiness
Piloerection of tail - anger, fear, excitement = “brush tail,” often with arched back and a hiss or screech

Social Behaviors
- Ferrets are also very social but can live well alone if given play time and human interaction
- Some fighting with new ferrets
- Can put Ferretone™ on neck of ferrets that are being introduced

Grooming Behaviors - Ferrets
- Self-grooming by licking and nibbling
- Mutual grooming especially around head and ears
- Trichobezoars are common
- Lack of grooming
  - Obesity
  - Arthritis or other pain
  - Discospondylosis
  - Orofacial pathology
  - Intense pruritus/parasites
  - Lethargy (insulinoma in ferrets)
  - Diarrhea/fecal matting

Eating Behaviors - Ferrets
- Obligate carnivore
- GI transit time = 3 hours
- Needs concentrated diet high in protein/fat and low in fiber
- Snack throughout the day; eat more and gain weight in winter
- Do not feed simple carbs or sugars
- Lack of food - polydipsia
- Lack of water - anorexia
- Counsel owners about how food and water are provided and maintained

Elimination Behaviors - Ferrets
- Defecation - look for a spot, back up (in a corner), arch back slightly with tail raised, do not bury feces, anal drag
- Urination - similar posture, rear feet spread farther apart, females squat lower, urine licking common
- Litter box for digging and playing

Locomotor Behaviors/Activity - Ferrets
- Alternate all four legs
- Hop or gallop in play
- Weasel war dance
- Alligator roll
- Slumping
- Usually sleep in a curled position
- Weakness in rear limbs is most common “lameness”
Play Behaviors
- Chase
- Exaggerated approach or ambush
- Veering off and reciprocal chase
- Mounting, rolling, wrestling
- Inhibited neck biting
- Accompanied by dooking (excitement) and hissing (anger)
- Digging - from burrowing behavior
- “Ferreting away” - objects of interest put away in small, dark places

How Does Behavior Relate to Hospitalization? - Ferrets
- Provide towels to burrow under
- Slings
- Litter box (no clay litter)
- Separate from predators
- Escape proof
- Obesity
  - Too much food
  - Too little exercise
  - Associated medical problems
    - Difficulty grooming
    - Difficulty ambulating
    - Pressure on GIT, diaphragm
    - Pododermatitis
- Pain
  - Know clinical signs of pain
  - Address pain before diagnostics and other treatments
  - Secondary physiological changes include gastric ulcers, decreased peripheral circulation, decreased temperature, GI stasis and even death

Aggression or Biting Behaviors
- Play aggression - mostly young ferrets
- Possessive aggression - favored toy
- Fear-related aggression - trauma/poor socialization
- Redirected aggression - as when separating ferrets that are playing
- Maternal aggression - to protect kits
- Pain-induced aggression
- Predatory aggression - stalking/chasing/grasping/biting
- Sexual aggression - intense neck biting
- Ferrets bite down, hold on and shake their heads

Managing Aggressive Play-Biting Behavior
- Avoid aggressive play and tug-of-war
- Keep fingers curled
- Redirect behavior
- High-pitched yip when bitten
- Scruff, wriggle and hiss
- Gentle cuddling inside a towel
- Time out
- Food treat when calm

**Behavioral Enrichment**
- Simulate natural environment
- Allow for play
- Bonded pairs/trios
- Provide UVB lighting?
- Counsel clients on how to best provide for their pet’s emotional and psychosocial needs
- Cardboard boxes
- PVC tubes
- Dryer hose
- Empty paper bags
- Straw mats and baskets
- Food treat in a plastic bottle or egg carton
- Telephone books
- Toys
- Toilet paper/paper towel tubes
- Ping pong balls in water
- Hiding toys in sandbox
- Suspend ping pong or plastic ball on string
- Paper bag filled with crumpled paper, ping pong balls or food treats
- Cardboard box filled with potting soil, rice, ping pong balls, hay or crumpled pieces of paper for digging
- Ball hanging from string so it is 2” from ground
Equine Parasites: Understanding the Culprits
Wendy M. Duckett, DVM, MSci, DACVIM (LA)
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OVERVIEW
This lecture will cover a selected number of the “Usual”, and a few “Not So Usual” suspects, including large and small strongyles, tapeworms, ascarids, bots, pin worms (Oxyuris), Strongyloides, lungworms, stomach worms, Onchocerca, eye worms and central nervous system nematodes. Information pertinent to clinical impact on their equine hosts and recognition of the diseases they cause will be covered. Knowledge of the parasites’ biological characteristics will help us be more accurate in our diagnoses as well as be more effective with our control strategies (covered in the subsequent lectures).

OBJECTIVES OF THE PRESENTATION
- Become familiar with selected horse parasites and their impact on the host.
- Become familiar with the parasites’ life stages to aid in more accurate diagnoses and to maximize the effectiveness of control strategies.

THE CULPRITS
The Large Strongyles: Strongylus vulgaris, S. edentatus and S. equinus
For over 200 years Strongylus vulgaris has been considered the most pathogenic and common parasite of horses. Only recently, with the introduction of ivermectin, has this changed. It may no longer be the most common but is still very pathogenic. Adult nematodes infest the large colon and cecum and because they are voracious plug feeders, heavy loads can cause anemia and disruption of the mucosa. It is, however the larval stages prior to the maturation of egg-laying adults in the colon that do the greatest damage. Migration through the cranial mesenteric artery (CMA) intima can result in severe arteritis, thromboembolism, colic and death due to ischemia of varying degrees of the small and large intestine (including cecum). Horses of all ages can be affected.

Severe gut compromise and death can occur before there are any egg-laying adults because the prepatent period (PPP) is long. At least 5–6 months for S. vulgaris, and up to 10 months for the others. Keep this in mind as young foals will have negative egg counts during this period. Other signs can include weight loss, diarrhea, unthriftiness, impaired absorption, possibly fever. Aberrant larval migration can include the CNS (central nervous system). Laboratory findings may include anemia, neutrophilia, eosinophilia, hyperfibrinogenemia, hypoalbuminemia and increased serum Ig(T).

Strongylus edentatus and S. equinus do not invade the mesenteric arteries but do migrate in the abdomen and have been found in the liver, pancreas, ventral abdominal wall and kidney.

The life cycle is direct, passing from pasture, to horse and back onto pasture via the manure and having no intermediate host. The majority of the strongyle biomass at any one time is on pasture. The eggs and larvae can survive in the manure on pasture for years and over winter. In order for the infection to be passed to other horses, development to the infective larva (L₃) must occur and it then has to be dispersed onto the forage.

The Small Strongyles: The Cyathostomes
The small strongyles are now (since the 1980s) considered to be the most significant internal parasite of horses. There are over 40–50 genera and species, with 10 or 12 of those being most prevalent. The life cycle is direct. Egg-laying adulthood is reached in the large colon after ingestion of infective stage larvae 5.5–14 weeks (PPP). The infective stage L₃ can become an adult in the large colon lumen, or can become encysted in the gut wall, embedding as deep as the intima. These encysted or hypobiotic larvae can
become dormant and remain for a couple of years or more. The buildup of larvae and the subsequent emergence can be devastating to the host.

Clinical issues range from unthriftiness, weight loss, hypoproteinemia, mild inflammatory enteritis, diarrhea, ventral edema, fever, colic, anorexia, emaciation, severe debilitation and death. Diarrhea can occur at the time of larval penetration as well as emergence from the gut wall. Laboratory findings can include hypoproteinemia, hypoalbuminemia, leukocytosis and elevated globulins. Larval emergence can cause outbreaks of colic/diarrhea in late winter, early spring. Deworming can stimulate emergence. Encysted strongyles are not laying eggs; therefore, low fecal ova counts can be deceiving.

The triggers for the larvae to become encysted and dormant are not understood. Some individuals seem more susceptible to disease. There is a phenomenon of innate resistance to the parasites/and or the damage they cause that occurs with age in the host. It appears to be important for youngsters to be exposed to some strongyles in order for that immunity to take place.

The adult worms are affected by benzimidazoles, pyrantels and ivermectin, but the encysted, dormant larvae in the gut wall are not affected by any of the anthelmintics except moxidectin and larvicidal doses of fenbendazole. Resistant populations are a significant issue.

**Tapeworms: Anoplocephala perfoliata, A. magna**
The presence of tapeworms in horses has been known for some time, but was not considered to be of clinical significance until recently. Not unlike the small strongyles, the tapeworms lived in the shadow of S. vulgaris, until ivermectin. And not unlike the small strongyles, they have had a chance to come into their own notoriety. Tapeworms are not affected by any of the anthelmintics except praziquantel or a dose of pyrantel (13.2 mg/kg) double the dose recommended for strongyles. So, while ivermectin takes care of the adult and most migrating larval stages of strongyles, the tapeworms are not affected. The adult tapeworms have a predilection to inhabit the distal ileum, ileocecal valve and cecum. Clinical issues of anemia, spasmodic colic, diarrhea, ileal impaction, perforation and ileocecal intussusception have been associated with tapeworm infestations.

The PPP is 28–42 days. Relying on fecal egg presence is not reliable for diagnostics, as tapeworms are not consistent egg shedders and modification of fecal flotation methods is helpful. There is a serum ELISA anti 12/13 KDa IgG (T) test that shows promise. It is not widely available at this time.

Tapeworms have an indirect life cycle. The intermediate host of horse tapeworms is the small, ubiquitous free-living orbatid mite, which the horses ingest while eating.

**Equine Hydatid Disease: Echinococcus granulosus equinum (Not So Usual)**
The definitive host of Echinococcus tapeworm is the dog (coyote, wolf, fox). Horses, people and other livestock can be accidental intermediate hosts. In these accidental intermediate species, the disease will be one of space-occupying cysts.

Echinococcus is present on every continent but Antarctica. The accidental hosts ingest the infective eggs from feces-contaminated food, fomites and dogs’ coats. Livestock ingest eggs from canine feces-contaminated forage or feed. The cysts can form in the brain, liver, and other organs. If the cysts become large enough, clinical signs consistent with a space-occupying lesion in the affected organ will become apparent. The life cycle does not complete in the intermediate host so the definitive host dogs become reinfected from ingesting carcasses of infected intermediate hosts.

In horses it is more common in Europe than North America. There is a report of a North American-born horse being infected, but most reports are from horses imported from Europe. It is most often an incidental finding at necropsy.

In endemic areas care should be taken in disposing animal carcasses to prevent ingestion by canines. The contents of the cysts are potentially infectious to people so care should be taken if they are
identified at necropsy. European species recently reported to be found in coyotes, foxes and dogs in Canada.

**Ascarids: Parascaris equorum**
This species specific roundworm is a significant issue for young horses. Acquired host immunity makes this infection rare in horses of 2 years of age and greater. Affected foals can have signs of unthriftness, pot-bellied appearance, rough hair coat, failure to grow, colic and occasionally intestinal perforation. Foals can exhibit respiratory signs of cough, fever and nasal discharge due to the migration of larval ascarid stages through the lungs which is part of the normal life cycle. The PPP is 10–12 weeks, so signs of infestation can occur before the feces are positive for eggs.

Ascarids have a direct life cycle. The hardy, sticky eggs can remain viable for months to years in the environment. Foals become infected shortly after birth from contaminated mare, water, feed and stalls. The stages inhabiting the small intestinal lumen are susceptible to piperazine, benzimidazoles, pyrantel, ivermectin and moxidectin. There are resistant populations in some areas. Migrating larval stages causing verminous pneumonia would have to be treated with ivermectin, or fenbendazole at accelerated doses (10 mg/kg body wt. for 5 days). It is recommended to start deworming at 2 months of age for ascarid control. It is recommended to use fenbendazole at 10 mg/kg body weight as ascarids are the dose-limiting parasites (DLP) for this anthelmintic.

**Bots: Gasterophilus spp.**
This common stomach parasite is the larval stage of the *Gasterophilus* fly. The adult flies, *G. nasalis, G. intestinalis* and *G. hemorrhoides*, have vestigial mouth parts, so they do not bite, but they are a nuisance as they lay eggs around the mouth, head, shoulders and forelimbs of the horses. They lay one egg per visit to the hair coat and each female can deposit up to several hundred eggs. The recognizable elongated, cream coloured eggs either hatch and make their way to the mouth or are licked off the skin by the horse, hatch and bury into the mucosa of the mouth where they spend about a month, then migrate to the pharynx and are swallowed.

The migrating 1st and 2nd instar (larval) stages can cause irritation and ulceration to the tongue and gums. Once swallowed, the 3rd stage larvae attach to the mucosa of the stomach (*G. nasalis* and *G. intestinalis*) or the duodenum and rectum (*G. hemorrhoides*). The most common site is the non-glandular (squamous) part but they can also attach to the glandular area of the stomach. They spend up to 12 months attached to the stomach. Few serious clinical sequellae are attributed to bots, but they have rarely caused stomach perforation or obstruction of the pylorus. They pupate and pass into the intestine and are expelled in the feces to complete the cycle, hatching as flies in the warm season.

Historically, carbon disulfide (CS₂) and organophosphates have been used to kill bots. More recently, ivermectin and moxidectin are used.

The adult fly stage of the cycle will be an issue depending on the length of fly season in each climatic zone. In temperate climates flies will be gone after freezing and not return until spring. The larvae winter comfortably in the horses’ stomachs.

**Pinworms: Oxyuris equi**
Ubiquitous nematode, living in colon and rectum. Gravid females lay eggs around anus and perineum, therefore eggs not usually seen in feces. Eggs are sticky and adhere to skin and environmental surfaces. Washing removes. Eggs hatch, become infective larvae in 3–5 days, contaminate stable, bedding, feed, water. Ingested, sexually mature within 5 months (maybe as soon as 3.5 months). Most signs attributed to irritation and severe itching (rat-tail appearance) elicited by deposited eggs. Most anthelmintics effective. Washing perineum will decrease egg numbers and help relieve itching.
**Strongyloides westeri**

*Strongyloides* infestations are not particularly common but can potentially be an issue for nursing and weanling foals. Large burdens of adult worms inhabiting the small intestine can cause diarrhea in foals as young as 9–14 days. Fecal egg (larvated) counts will be positive at this time. Heavy infestations may persist until immunity develops by 15–23 weeks of age. Foals are the source of infective eggs in the environment as mares do not usually have patent infections. The mares can have encysted larval stages that are stimulated at parturition and infective larval stages are passed to the nursing foal via the milk. Foals can also be infected by ingesting the infective eggs shed by other foals. Adult worms are susceptible to oxibendazole and ivermectin. Ivermectin and moxidectin will kill adults as well as encysted larvae.

**Lungworms: Dictyocaulus arnfieldi**

While ascarids and *Strongyloides* migrate through the lung parenchyma on their way to the gut and sometimes cause respiratory signs in foals, adult *Dictyocaulus* nematodes reside in the airways and can cause increased respiratory rate, cough and bronchitis in horses.

Donkeys and mules, the natural hosts, remain asymptomatic but are most commonly the source of infection. The life cycle is direct. The PPP is about 4 weeks. The infection is not always patent in horses; therefore, the donkeys/mules should be tested. Fecal egg counts will be negative because it is the first stage larvae that are passed in the feces so negative fecal egg counts does not rule out lungworms. The eggs are larvated and hatch in the bronchioles, they are coughed up and transported up the bronchociliary blanket to the pharynx and swallowed. The feces can be tested for the larvae by a Baermann technique. Larvae and/or larvated eggs may be found in tracheal wash samples in the affected horses.

Ivermectin moxidectin, fenbendazole and levamisole are effective against lung worms.

**Stomach Worms: Habronema spp., Draschia megastoma, Trichostrongylus axei**

*Trichostrongylus axei* is mainly a parasite of ruminants but can infect horses sharing pasture with sheep or cattle. In large numbers a chronic gastritis with mucous production resulting in weight loss can be an issue. Eggs are shed in the feces but are not distinguishable from strongyle eggs. Some benzimidazoles, ivermectin and moxidectin are effective against these stomach worms.

*Habronema* and *Draschia* are nematodes with indirect life cycles involving fly intermediate hosts. The adult nematodes reside in nodules or freely on the stomach mucosa. Eggs are passed in the feces. Eggs and larvae of the stomach worms are ingested by maggots of house or stable flies. Horses are infected by ingesting infected flies or L1 larvae. *Habronema* flies feeding around mucocutaneous areas or wounded skin deposit larvae which cause disfiguring granulomatous masses (summer sores). These can be confirmed histologically. The eggs are not usually identified in feces because they have thin walls which readily collapse. Fly control, wound debrideement and treatment with ivermectin, moxidectin, organophosphate or diethylcarbamazine (DEC) will help treat/prevent this disease.

**Onchocerca: O. cervicalis, O. reticulata**

Adult nematodes have a life span of up to 5 years and live hidden in the connective tissue of the nuchal ligament (*O. cervicalis*) or ligaments and tendons of the distal limbs (*O. reticulata*). The females produce microfilaria, which are associated with dermatitis and ocular lesions.

There is an arthropod intermediate host, the biting midge, *Culicoides*, which ingest microfilaria while feeding. Classically, the lesions are along the ventral midline of the abdomen and on the face. Some horses manifest a sensitivity to the midges, which causes a seasonal pruritic dermatitis.

Horses greater than 5 years of age are more likely to be affected. Areas of alopecia on the face and midline are seen. Granulomatous reactions can be seen in the limbus of the eyes. The association of
Onchocerca with cases of uveitis is still debated. A flare up of uveitis has been reported after deworming with Ivermectin if microfilariae migrating in the eye are killed. Edema of the ventral abdomen and/or face will be seen following the kill off of microfilaria in the skin after deworming with Ivermectin. A diagnosis can be suspected based on clinical signs, a history of not being dewormed with Ivermectin and the presence of microfilaria teased from skin biopsies. Individuals may harbor the microfilaria without showing signs.

In the past, levamisole, organophosphates and diethylcarbamazine have been used to kill microfilariae.

Verminous Encephalomyelitis: Some of the “Not So Usual” Suspects
Halicephalobus gingivalis (Micronema deletrix), is a free-living, soil-borne saprophyte, which has been found to cause disease after infesting the central nervous system (CNS), uvea, kidney, nasal cavity and gingiva (granuloma) of horses. Strongylus vulgaris larvae can infest the CNS of horse during aberrant migration. Setaria (Kumri) larvae of this parasite which resides in the abdominal cavity can also occasionally invade the CNS. It is transmitted by mosquitoes. The larvae can also cause cutaneous posthitis. Parelaphostrongylus tenuis, which is the brain or meningeal worm of white-tailed deer, can infect atypical hosts including horses and camelds. Horses can develop sudden onset torticollis due to P. tenuis infection of the spinal cord.

Clinical signs include ataxia, posterior paresis, depression, recumbency, blindness, uveitis, posthitis, circling, dementia, dysphagia, usually asymmetrical, and other neurological conditions must be ruled out. CSF tap findings may or may not include eosinophilia, neutrophilia, xanthochromia, increased protein so findings are not specific. Treatment should include supportive treatment for neurological inflammation. Fenbendazole 50 mg/kg orally once daily for 3 days can be used. Ivermectin may be effective. Killing is delayed with ivermectin.

Eye Worms: Some of the “Not So Usual” Suspects
Thelazia lacrimalis adults infest the conjunctival and lacrimal sac of horses. The worms can be seen on the corneal surface. The female worms lay larvae, which are transmitted by face flies (Musca autumnalis) as they feed on eye secretions.

Clinical signs include tearing, conjunctivitis corneal edema and corneal ulcers in advanced cases. Worms can be manually removed after instilling drops of local anesthetic in the eye. Fly control will help prevent spreading. Ivermectin and larvicidal doses of fenbendazole can be used for treatment. Setaria spp. adults reside in the abdominal cavity on the serosal surfaces. They are slender, white and several cm/ to inches long. They can be encountered while doing a laparotomy. Microfilariae can show up on blood smears. Aberrant larval migration can result in this parasite being found in the anterior chamber of the eye, as well as CNS as previously discussed. They are not common since the wide use of ivermectin.

Liver Flukes
Fascioloides hepatica and F. magna infestations have been reported in horses. A combination of wet, marshy conditions and the presence of the snail intermediate host must be present. The natural host of F. magna is the white tailed deer. Summer drought and winter cold disrupt the life cycle. Chronically infected sheep are a source of F. hepatica on pasture. Even then, infections are more common in ruminants than horses. Horses can have liver flukes that are found incidentally at postmortem or with clinical liver disease. In January 2006, a fluke ban was put in place in Western Australia. Horses for import had to be kept on high, dry ground and treated with 12 mg/kg triclabendazole.
Signs can include anemia and icterus. Nodules, cysts, necrotic tracts and the flukes can be found at postmortem. Liver enzymes will be elevated. Infections are non-patent, so fecal floats for diagnosis are unreliable. Heavy loads will be found in ruminants grazing the same pastures.

Control for horses is to avoid infested ruminants, wet areas, snails and white tailed deer. Flukicidal drugs include albendazole, triclabendazole, oxyclozanide and levamisole, but these drugs are not without side effects.

REFERENCES

References are provided on request.
Equine Parasite Control Strategies: Anthelmintics - Old and New
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Overview
Anthelmintics have been a significant tool in controlling and treating horse parasitism particularly since the 1940s. They reached their heydays in the 1970s and 80s with the advent of safer and more effective compounds. No new major families of equine anthelmintics have been introduced for several years. This is a major concern, as there is a rising issue of parasite resistance against some drug families.

One trend that has occurred in the world of deworming, is the distancing of veterinarians since the 1970s from close involvement with decision making and anthelmintic administration as veterinarians are no longer stomach tubing and the owners are buying over the counter oral dewormers. Owners sometimes have misconceptions about parasites and the dewormers and it is important especially with the rising problem of resistance that veterinarians stay armed with information and be involved in program decisions.

Because availability and labeling claims can vary among countries and change over time, always defer to the manufacturer’s recommendations concerning dosing, spectrum of activity, efficacy, safety and contraindications. Abide by recommended withdrawal times for horses intended for human consumption to avoid food residues.

Objectives of the Presentation
- Review each anthelmintic family and be reminded of the correct indications for use and potential side effects
- Discuss issue of resistance and strategies to recognize and minimize resistance

Historically, horse parasites have been an issue and attempts to control them have been a concern for hundreds of years. Treatments have included a range of substances from eggs, birds’ intestines, calomel, aniseed, aloes, antimony, licorice, linseed, vitreolated quicksilver, tobacco, garlic, onions, pumpkin seeds and wormseed oil (Chenopodium). The effects also ranged from questionable efficacy to downright nasty. Sometimes the side effects were more harmful than the parasites.

The earlier anthelmintics tended to be less efficacious and required relatively large volumes and the mode of administration for years was via nasogastric intubation. Newer drugs became more potent, allowing smaller volumes and oral administration became feasible. A very effective intramuscular form of ivermectin was on the market for 10 months in 1984, but horse deaths from associated clostridial myositis resulted in discontinuation of the product.

Horse owner misconceptions regarding parasites and dewormers:
- Rotating dewormers means choosing a different colour label or brand name each time
- One syringe is a correct dose for one horse
- All dewormers kill all parasites
- All horses have all parasites and shed eggs equally
THE ANTHELMINTIC FAMILIES

Carbon Disulfide (CS₂)
Introduced as a dewormer in 1917 to treat bots and ascarids, this compound was found in commercial products as a boticide up into the early 1980s. Although effective against bots, it had a narrow safety margin, could be hepatotoxic, and smelled like rotting cabbage.

Phenothiazine
The antiparasitic properties of phenothiazine were identified in the 1930s. It was effective against adult strongyles, thus revolutionary for its time. Side effects included sporadic cases of photosensitization and hemolytic crises. Phenothiazine remained in deworming combinations until the mid-1980s.

Piperazine
The antiparasitic properties of piperazine were described in 1949. It is still available today. The mechanism of action is as a GABA (gamma amino butyric acid) agonist. GABA is an inhibitory neurotransmitter, thus the parasites become paralyzed. Also it causes spastic paralysis by blocking acetylcholine in the parasites. It has a narrow spectrum, killing adult worms only of ascarids, pinworms and cyathostomes. Fairly large volumes are needed to be effective. It is available as liquid or powder and was used in combination anthelmintics formulated to be administered via nasogastric tube. It could be useful against benzimidazoles-resistant cyathostomes. Piperazine can develop its own cyathostome resistance.

Diethylcarbamazine (DEC) is a relative of piperazine and has filaricidal properties. It has been used in the management of summer sores (Haemonema) and onchocerciasis in horses in the past. It has antinflammatory properties against leukotrienes (previously slow-reacting substance of anaphylaxis or SRS-A).

Organophosphates
One of the narrow-spectrum dewormers marketed as a boticide alone or in combinations. It was the mainstay for treating bots between the CS₂ era and the ivermectin era. It has activity also against some strongyles as well as Haemonema. The mechanism of action is an anticholinesterase in the parasites, as well as in the host, so dosage is crucial. The toxicity is potentiated when administered in conjunction with phenothiazine compounds, which include acepromazine tranquilizers. Trichlorphon can still be found on the market.

Benzimidazoles
The benzimidazole dynasty started with thiabendazole in 1961. Safer and more broad spectrum than phenothiazine, derivatives of this family are still used widely. Examples are fenbendazole, oxibendazole, oxfendazole, mebendazole, cambendazole, albendazole and triclabendazole. Their parasitic spectrums vary; refer to manufacture label information for specifics. The mechanism of action is by inhibition of microtubule formation, which prevents reproduction and digestion in the parasites. It also can kill parasite eggs. It has a slow onset of action. In general, they are effective against adult large and small strongyles, ascarids to a degree, and pinworms. Ascarids are the DLP (dose-limiting parasite) for benzimidazoles, so 10 mg/kg rather than the standard 5 mg/kg dose is used.

Fenbendazole at an accelerated dose of 10 mg/kg PO for 5 days is used to kill larval stages of strongyles. At 10 mg/kg, fenbendazole is effective against ascarids. The dead worms tend to be flaccid and pass more readily than ascarids killed by piperazine or ivermectin which tend to be rigid.

Oxfendazole and oxibendazole are also effective against lungworms.
Triclabendazole and albendazole have flukicide properties.
Febenatal is a prebenzimidazole, which is metabolized to benzimidazole after being administered.
Pyrimidines
Pyrantel pamoate, tartrate and embonate. Introduced in the 1960s and still in common use. Pyrantel tartrate is a daily dewormer. Pyrantel pamoate is an interval dewormer. The mechanism of action is spastic paralysis of the parasites’ muscles via acetylcholine stimulation. They are safe for pregnant and lactating mares, stallions and can be started in foals at 2–3 months of ages. The duration of effect is 4–6 weeks. Effective against adult nematodes at label dose, pyrantel pamoate is effective against tapeworms at 13.2 mg/kg (twice nematode dose).
Daily pyrantel tartrate prevents strongyles and ascarids. Initial deworming and periodic deworming against bots and tapeworms is required. It is not for use in horses intended for food.

Imidazothiazoles
Levamisole introduced in the mid-1960s is an isomer of tetramisole, which is used as a dewormer in food animals. It causes neuromuscular paralysis in the parasites. It is effective against adult nematodes.
Levamisole also has immunomodulating properties, stimulating cell-mediated immunity, and has been used as an adjunct therapy in treating heaves and equine protozoal myeloencephalitis (EPM) in horses, and toxoplasmosis in people.
It adversely reacts with pyrantel, DEC and organophosphate to potentiate toxicity. Signs of toxicosis include salivation and tremors. It may cause blood dyscrasias in people through contact. It cross-reacts on blood test to aminorex, a banned substance in race horses in Canada.

Macroyclic Lactones
Ivermectin was introduced in 1981. The safest, most potent, broadest spectrum anthelmintic yet. A revolutionary anthelmintic as its wide usage and effectiveness against the devastating migrating larval stages of the large strongyles brought them under reasonable control. This marked the rise of the small strongyles to the station they hold today as the most common equine parasite problem.
With the introduction of the macrocyclic lactones, the spectrum truly broadened as they are effective against bots, as well as the nematodes, ascarids, pinworms, strongyloides, external parasites, lungworms, Onchocerca microfilaria and stomach worms. The only major group of parasites that they do not kill are the tapeworms. They also are not effective against flukes. The duration of action is 6–8 weeks. The mechanism of action is paralysis of the parasites via interference with chloride channels and stimulation of GABA (inhibitory) neurotransmitters. There may be transient swelling of face and ventrum if large numbers of Onchocerca microfilaria are killed, and/or transient swelling of the lips and mouth along with salivation if bot phases are killed within the mouth.
Ivermectin is toxic to aquatic life in the environment. It has a wide margin of safety in the horse. Cases of toxicosis do occur particularly in foals, where there is a greater chance of ivermectin crossing the blood brain barrier (BBB). Also, inadvertent overdosing in foals and miniatures can result in toxicosis. The animals will be lethargic, recumbent, comatose, and may have seizures. Supportive care can be successful, depending on the amount of overdose. The use of diazepam (Valium) is contraindicated in treating ivermectin overdose as it also stimulates GABA neurotransmitters and will worsen the signs.
Toxicosis at therapeutic levels ingested concurrently with Solanum spp. plants is reported (Norman et al. 2012).
Moxidectin (milbemycin) is the second macrocyclic lactone dewormer on the market for horses. It essentially has the same properties as ivermectin, but there is a longer period of action, up to 12 weeks, and it is also effective against the encysted stages of small strongyles. It is not currently labeled for use in foals less than 4 months of age. It is not to be used in horses intended for food. The toxicity comments for ivermectin apply to moxidectin.
**Isoquinolones**

**Praziquantel** is the most recent class of dewormers approved for equine use on the market. It is a narrow-spectrum drug with the primary target being tapeworms.

Its mechanism of action is to increase calcium absorption by the worms, resulting in muscle contraction and paralysis. It is available in combinations with ivermectin and moxidectin.

**New Anthelmintics: Amino-Acetonitrile Derivatives (ADDs)**

Monepantel and derquantel. Since 2010, new drugs effective against resistant nematodes marketed for **ruminants only.** Derquantel has been reported to be toxic to horses.

**Combinations**

Combination preparations are used to achieve a broader spectrum against the major parasite groups. One of the first, for instance, was a combination of phenothizaine, (for the adult strongyles), piperazine (for the roundworms), and CS₂ (for bots). Combinations were also used to slow down the emergence of resistance.

Combinations such as ivermectin and praziquantel are currently available to increase the spectrum of efficacy to include tapeworms. Using combinations also allowed for some individual components to be used at lower doses and thus decrease the chances of adverse side effects. Some combinations have synergistic effects. For example there seems to be a synergistic effect is with the combination of oxendazole and pyrantel (at a dose appropriate for killing tapeworms).

**Alternative Dewormers**

There is interest in alternatives to the chemical dewormers. Organic, herbal and natural compounds, if found effective, would eliminate the environmental issues and be more desirable for many owners. There is a lack of critical studies to prove or disprove efficacy. One substance that has been looked at is silicon dioxide or diatomaceous earth (DE). There is no evidence of efficacy.

**Resistance**

Resistance of the small strongyles to phenothiazine became apparent in the 1950s and subsequent resistance to the benzimidazoles became apparent in the 1960s. Oxibendazole may be one of the last drugs of the group to which the strongyles become resistant. Pyrantel resistance in small strongyles has been reported recently (Brazik et al. 2006).

Evidence of resistance of ascarids to macrocyclic lactones has occurred (Woods et al. 1998). There is currently one report of moxidectin-resistant small strongyles in a donkey herd in the UK (Trawford et al. 2005). A shortened strongyle fecal egg count reappearance interval following ivermectin administration has been reported in Kentucky (Lyons et al. 2008). Eggs started reappearing by 4 weeks.

**Recognizing Resistance**

- Persistence of parasite-related clinical issues in the face of deworming
- Failure of anthelmintic administration to result in a decrease of the FECs
- Shortened egg reappearance intervals after anthelmintic administration

**Fecal Egg Count Reduction Test (FECRT)**

An FECRT of less than 85% is indicative of developing resistance
**Mechanism of Resistance**
Resistance traits are inherited. Resistance development requires the presence of resistant genes, and the rate of resistance development in a population depends on the selection pressure of the surviving worms to pass them on (Sangster 1999). Once a population of parasites are resistant, it can remain that way for years (Slocombe et al. 2008).

**Strategies to Reduce the Risk of Resistance**
- Avoid using anthelmintics and use alternative management strategies described in the previous session.
- Know the status of new horses coming on to your premises so that you do not introduce resistant populations on to your farm. Separate new horses, do fecal FEC monitoring before and after deworming.
- Do not underdose or use half doses, this encourages resistance.
- Rotation of drug classes shows some evidence of slowing down resistance, at least short term or fast rotation (Blanek et al. 2006). The benefit of longer term or yearly rotating is not definitively known, and the rotation issue is still under debate. Rotating away from the macrocyclic lactones as long as you still have a sensitive population decreases the selection pressure for resistance. Because they kill more stages of the parasite (refugium), the macrocyclic lactones exert greater resistance selection pressure.
- Use combinations of drug classes.
- Decrease the amount of anthelmintic usage and spread out the deworming intervals as much as possible based on FEC monitoring. The shorter the deworming frequency, the more selection pressure for resistance (Sangster 1999).
- Avoid deworming when the parasites in refugium are at their lowest (winter in cold climates, summer in hot climates). Selection pressure for resistance is high if deworming at those times.
- Selectively deworm the heavy shedders utilizing FEC data. This reduces the risk of clinical disease in the most at risk horses but does not put selection pressure for resistance on the refugia.

**REFERENCES**
References are provided on request.
Equine Parasites: Management Strategies for Parasite Control
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OVERVIEW
This session will discuss strategies that can be applied to control the transmission of parasites among horses. Targeting the parasites while they are within the horse (host factors) and outside the horse (environmental factors) will be discussed. Environmental factors include issues with manure, composting, pasture, stall, season, climate, intermediate hosts and other species. Host susceptibility, the usefulness and limitations of fecal flotation and egg counts, and the crucial principles of anthelmintic use will be discussed. The principles and importance of the parasite refugium and its relevance to anthelmintic resistance will be introduced.

OBJECTIVES OF THE PRESENTATION
Become familiar with control strategies and principles, their advantages and disadvantages to be able to apply them appropriately

ENVIRONMENTAL FACTORS
Being able to effectively use environmental control measures can help reduce the amount of anthelmintic drug use and delay resistance.

Manure
Because many of the equine parasites have direct life cycles with stages being passed from the host to the environment in the feces, and some parasites find manure a haven of survival of infective stages and the intermediate hosts and transmitters of some parasites (flies) live in manure, it is an obvious but challenging target for control.

The obvious control principle is to remove manure from the vicinity of housed and pastured horses. Picking manure manually is effective but labour intensive. Pasture vacuums can be effective but expensive and not feasible for many pastures. A study done in Newmarket in the 1980s showed twice-weekly pasture vacuuming to control strongyle infectivity. Horse diapers are available for selected situations (www.equisan.com.au/).

Feeding from raised feeders can help decrease the contact of feed to manure contamination.

Dung Beetles
Dung beetles lay their eggs in manure, break up the pile and bury it in the ground. Because fecal piles are an excellent reservoir of infective parasites and fly larvae, dung beetles are a natural means of manure, fly and parasite control. There are cool and warm weather species of dung beetle. They are active year round in warm weather. Ivermectin is toxic to immature beetles, moxidectin less so. After deworming, manure may be toxic to young beetles for up to 6 weeks. Deworming in fall after first frost and early spring before warm weather will not affect beetle activity. Studies assessing the ability of beetles to reduce infective larvae have shown variable results. One short-term Texas study showed enhanced hatching of larvae. Another study reported decreased survival of larval stages in warm, subtropical climates.

Composting
Composting can be an effective way of keeping feces away from the feeding areas and a means of killing infective eggs and larvae when temperatures reach 32–60°C (90–140°F). The volume of the manure decreases with proper composting and then can be spread on pasture or hauled away. Do not spread
uncomposted manure on pastures as it is source of infective parasites and it utilizes more soil nitrogen to decompose. Enough space to locate manure piles to minimize attracting flies and to avoid contaminating ground water can be a huge challenge. Guidelines for proper composting techniques are available. One reference is www.manuremaiden.com/resources (VIN editor: link was edited as of 4/1/13).

**Pasture Management**

Pasture has a significant potential for strongyle infection to occur as the largest amount of the total parasite biomass exists on pasture, not in the host. The proper **stocking density** will depend on the quality of the pasture, geographic location, number of animals and available acreage. As long as the areas where the horses eat (referred to as “lawns”) remains separate from the areas where they defecate (called “roughs”), the stocking density is good. When the horses are forced to graze into the “roughs,” the stocking density is too high. Infectivity of strongyles is 15% higher in the roughs than the lawns (Herd 1980). Do not **harrow/mow pastures** as it just contaminate the grazing areas, unless after significant pasture rest in the hot dry season when it is certain the larvae are exposed to desiccation and sunlight. Adequate **pasture rest** may not be feasible as infective larvae can survive long periods and pasture land may be limited. At least 2 weeks to 2 months of rest in hot dry season in the south and 4 weeks to 2 months in the hot dry season in the north is recommended.

**Rotating** horses with ruminants on a pasture can be a strategy providing the ruminants are not carrying huge *T. axei* or fluke burdens. Rotating grazing with hay making can be useful in decreasing pasture burdens of infective larvae.

Avoid grazing wet, marshy areas where flukes are an issue.

**Stalls**

Whereas pastures are the primary source of strongyle infection, contaminated stalls are the major source of ascarid and *Oxyuris* (pinworm) infection. The infective stages of ascarids and pinworms are the eggs, which are more difficult to kill with disinfectants than are larvae.

**Insect Intermediate Hosts and Transmitters**

Insect intermediate hosts and transmitters were identified for certain parasites in the first lecture: Face or autumn flies (*Thelazia*), house and stable flies (*Habronema* and *Draschia* spp.), *Culicoides* gnats (*Onchocerca*), Orabatid mites (tapeworms), mosquitoes (*Setaria*) and Bot flies. Insect control is tied to manure handling, both of which are challenging. Strategies for insect control include the use of face masks, repellants, providing shade/shelter during fly season, keeping horses inside at peak insect feeding times (dawn and dusk for Culicoides). Face flies avoid entering dark shelters until they are seeking an over wintering place in the autumn. Bot fly egg removal can be a part of routine grooming. Orabatid mites are small and ubiquitous thus control not feasible. These mites are active, feeding and ingesting tapeworm eggs during warm summer and fall weather. The tapeworms likely survive in the mites overwinter.

**Other Intermediate Hosts and Species**

Avoidance of other intermediate hosts may or may not be feasible. The species and the parasites they can harbour that can be transmitted to horses are white tailed deer (*P. tenuis* and *Fasciola magna*), slugs and snails (*P. tenuis* and *Fasciola*) and ruminants (especially sheep) with heavy burdens of *Trichostrongylus axei* and *Fasciola hepatica*. Mules and donkeys are asymptomatic reservoirs of lungworms.
Season/Climate
Climate and geographic locations vary as to length of warm, hot, cool and cold seasons, moisture, rainfall, snow cover and insect season length. All these factors influence the challenges of parasite control. Climatic conditions influence parasite loads and infectivity in the environment. Free-living stages can survive in the environment, but they must be dispersed and transmitted to the horse in the infective stage (infectivity). Optimal temperatures for the development of strongyle eggs and larvae are 25–33°C (77–91°F) (Nielsen et al. 2006). At 28°C infective larvae developed in 4 days. Death occurred at 40°C (104°F) and embryonation ceased at 4°C (40°F). Cooler weather encourages persistence. The rate of infectivity of strongyle larvae increases as temperatures increase. Rainfall disseminates infective larval stages and drought hinders them. At high temperatures, moisture is more detrimental to survival than is desiccation (Hutchison et al. 1989). Desiccation is protective of freezing. The larval stages are more dependent on moisture than are the eggs. A rainfall of 1 inch or greater is an effective disseminator of larvae. In colder climates, the build-up of strongyle stages is in spring and summer. In hot climates, the build-up is in winter. Free-living strongyle stages survive cold winters in manure, but the infectivity is low, so there is less risk of infection. Hot weather decreases survival and infectivity.

Horses in hot climates are more at risk to infection in the winter. Horses in colder climates are more at risk in the summer.

Infectivity is low in the winter in Northern climates and low in the summer in Southern climates. Clean stalls are not conducive to strongyle transmission. Stalling horses can be a reprieve from strongyle transmission during times of high infectivity.

HOST FACTORS

Individual Variation
Some individuals seem to have an innate resistance or decreased susceptibility to heavy parasite loads and/or to the manifestation of clinical disease. Eighty percent of the worm burdens are carried by 20% of the horses.

Age
Younger horses tend to get larger parasite burdens. Commingling age groups is discouraged. Use of the cleanest pastures and stall hygiene is especially crucial for foals. Anthelmintics tend to be less efficacious in younger horses (Herd and Gabel 1950). There is a shorter egg reappearance period in yearlings than adults after anthelmintic use. There is a tendency as horses age to be less affected by the clinical diseases of parasite infestation (strongyle) burdens cause. Immunity develops against Strongyloides westeri by 6 months of age and ascarids usually by 2 years of age.

Other Diseases
Individuals with systemic conditions such as PPID (pars pituitary intermedia dysfunction) may carry heavier burdens associated with immune suppression.

Fecal Egg Counts
Fecal floats and egg counts (eggs per gram = EPG) are useful tools, which aid in the diagnosis and control of parasitism and identification of resistance. Interpretation is most reliable when we keep in mind the prepatent period (PPP) of the suspected parasites, the variation among parasites in fecal egg shedding, the seasonal variation in shedding and the individual variation amongst individual horses and animals of different ages to carry different parasite burdens within a group of horses. In colder climates, strongyle shedding increases in spring, summer and fall and decreases in winter. In hot climates, strongyle shedding peaks in winter. Encysted or hypobiotic small strongyles are not laying eggs. Tapeworms (and to some extent ascarids) are notoriously inconsistent egg shedders. For strongyle ova, 20 to 30 % of the
group can be high shedders (> 500 EPG), 30 to 50% low shedders (≤ 150 - EPG), and the remainder moderate shedders (150–500 EPG).

Fecal egg counts of less than 200 EPG have been correlated with a decrease in clinical colics (Uhlinger).

Identifying the heavy shedders and determining the egg reappearance intervals between dewormings can help in making strategic plans for control. Checking egg counts before and after deworming will determine if the program is working.

Egg reappearance intervals are currently (providing there is no resistance) 4 weeks for benzimidazoles and pyrantels, 6 to 8 weeks for ivermectin and 12 weeks for moxidectin.

**REFUGIUM**
The total parasite load on a premise includes the sum of what is in the environment (the majority) plus the load within the horses. After anthelmintic administration, the stages that are not affected by the treatment (environment, hypobiotic encysted phases) are referred to as the “refugium” or the “parasites in Refugium.” It’s a fun word, but so what? The parasite pool in refugium is a major factor in maintaining a genetic pool of parasites that remain sensitive to the available anthelmintics. The greater the stages of the parasite in refugium, the less likely they are to develop resistance in a population. One of the goals of parasite control is not to totally wipe out or sterilize animals of parasites, but to keep the level of parasites low enough that disease is a minimal issue and susceptibility to the dewormers is not lost. The serious issue of anthelmintic resistance is discussed further in the anthelmintic session. Another reason for not sterilizing the horses and environment of parasites is so that foals exposed to a few strongyles will then have the immune stimulation to develop their innate host resistance without exposing them to large loads associated with serious disease.

**DEWORMING THE HOST**
Commercial anthelmintic drugs marketed for deworming horses have been on the scene for less than 100 years. Novel or alternative dewormers were used prior to “modern” parasiticides and several substances are used as alternatives for reasons such as preventing environmental contamination and dealing with anthelmintic resistance. There are herbal or natural substances available. Critical trials are scarce and efficacy claims are lacking or anecdotal.

Trials feeding horses a naturally occurring, nematophagous fungus named “Duddingtonia flagrans” have been done in Europe, North America and Australia. *D. flagrans* is a fungus that when fed to horses traps and consumes parasitic larvae. It was found to reduce free-living L1 strongyle phases on pasture (Baudena et al. 2000). It was found to effectively reduce pasture larval load in cold climates. Safety trials have been done, but a commercial product is not on the market at this time.

**Principles of Anthelmintic Use**
Anthelmintics will only be efficacious if used and dosed correctly. Accurate body weight or estimation must be used. Underestimating will result in treatment failure and encourage resistance and overestimating will be wasteful and may increase the risk of toxicosis. Weigh scales or a weighbridge is accurate but not always available. Weight tapes are useful and inexpensive. They may be in the vicinity of 100 pounds inaccurate, but will provide better than guessing. Formulas using heart girth circumference and length from point of shoulder to point of the tuber ischium are useful:
Check the weight dosage on the package. One syringe of past dewormer ≠ one animal (mini, foal, pony, draft, warm blood) in many cases.

- Treat for the appropriate parasites according to age.
- Use the appropriate anthelmintic (drug class) for the parasite present or presumptive parasite.
- Always check manufacturer’s recommendations and contraindications (i.e., for safety in foals, pregnant mares, drug interactions, food residues).

**Frequency of Deworming**

Dewormers can be given on a **daily basis** or more commonly, intermittently. Daily deworming may interfere with normal development of immunity to strongyles and ascarids in young horses. The pressure for resistance to develop is moderate to heavy.

Intermittent or **interval** (purge) deworming can be on a regular year round basis or targeted for specific seasons.

Daily deworming programs are limited to one drug, pyrantel tartrate.

Interval deworming relies on knowledge of the egg reappearance interval to determine frequency of administration. Over the past few decades, it has been standard practice to deworm at intervals on a year round basis every 6 to 8 weeks. This regimen of deworming comes with a heavy selection pressure for resistance.

**Targeted or strategic** deworming is a more recent advent, based on the understanding of refugia, age and individual variations in parasite loads, utilization of FEC monitoring and knowledge of climatic and seasonal influences on the infective strongyle load of the pastures. Targeted or strategic deworming programs have less pressure to select for resistance, save on the cost of anthelmintics, involve the veterinarian more in planning and being involved in doing FECs. Strategic use of dewormers is timed to coincide with the rising infective parasite load, which coincides with the time of greatest risk of infection for the horse. For cold climates, that is summer. Deworming is done at intervals over the spring, summer and fall, which helps prevent the build-up of heavy loads on pasture, keeps resistance pressure down and reduces total number of treatments in a year.

In hot climates strategic deworming will be done through the fall and winter when infective stages are rising and the horses most at risk.

**References**

References are provided on request.
Induction Options and Cardiorespiratory Effects of Injectable Anesthesia
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INTRODUCTION
Horses frequently undergo field surgery with an injectable anesthetic regime. Field anesthesia is best suited for short elective surgical procedures to minimize anesthetic risks in an uncontrolled and unsupported environment. An adequate plane of anesthesia must be achieved to facilitate surgery and provide analgesia. In horses, field anesthesia imparts some unique considerations and concerns. Problems encountered are due to the risks and effects of producing recumbency, such as injury to the horse or handler as well as negative gravitational effects on the respiratory, cardiovascular and muscular systems. Short-term maintenance of field anesthesia is necessary to minimize the negative cardiorespiratory effects in the horse.

EQUINE FIELD ANESTHESIA

The Risk
When any animal is anesthetized there is a risk of development of minor complications, serious complication or even mortality. This is true for all anesthetized animals however equine anesthesia carries a relatively high mortality rate of 1% or approximately 1:100 horses compared to 1:10 000 in people, 1:1483 in dogs, and 1:2065 in cats. When sick horses and foals are included in this data, the equine mortality rates may be as high as 1:50 or 1:28 horses. It must be remembered though that these rates include anesthetic, surgical and recovery causes of death (bleeding, fractured limbs, shock). When only anesthetic causes are considered the equine mortality rate is closer to 1:1250. Regardless, maintenance with inhalational anesthesia carries a threefold higher risk of death than injectable anesthetics. These findings likely reflect the fact that injectable anesthesia is typically performed in the field on healthy horses for short durations, and do not mean that injectable anesthesia is without risks. Overall, age, disease, duration of anesthesia and anesthetic regime will impact the equine mortality rate. In the field, duration is a key factor.

Anesthetic complications can occur during induction, maintenance or recovery from equine anesthesia. Complications for field anesthesia in horses include inadequate chemical restraint, excitement, intra-arterial injections, muscle twitching, hypoventilation, hypertension/hypotension, bradycardia, tachycardia, hypoxemia, hypercarbia, corneal drying, corneal ulcers, excessive or inadequate anesthetic depth, jugular vein thrombophlebitis, lacerations, neuropathy, myopathy, inability to stand, and fractures to name a few. The goals of the practitioner for equine field anesthesia should include efficiency, organization, accurate dosing, and effective monitoring to minimize the chance of any of these complications in the field. Despite advancements in equine anesthesia with monitoring and supportive measures specific equine issues arise. Knowledge of specific equine considerations for field anesthesia is important.

Specific Equine Considerations

Hypoxemia
With a horse in recumbency relative hypoxemia (PaO₂ < 80 mmHg), or absolute hypoxemia (PaO₂ < 60 mm Hg) can develop. Hypoxemia primarily occurs due to ventilation and perfusion inequalities (termed V/Q mismatch) and intrapulmonary shunting of blood. This can occur with a horse under inhalant anesthesia and delivery of the inhalant with 100% oxygen or with field injectable anesthesia with the horse breathing room air (~21% oxygen). This is one of the main reasons why the time for field anesthesia should not be prolonged to > 35–45 min without supplemental oxygen. Horses tend to tolerate short-
duration hypoxemia well, that is they recover! Having said that, when monitored some horses can have a significantly reduced PaO₂ to as low as 40–50 mm Hg. These reduced levels of oxygenation will undoubtedly reduce tissue oxygen delivery and may impact how the horse may recover.

**Cardiovascular System**
Injectable field anesthetic techniques with an alpha₂-agonist, diazepam and ketamine regime, does not cause hypotension when dosed appropriately. Hypotension (MBP < 60 mm Hg) commonly develops under sole inhalational anesthesia in horses even with surgery necessitating blood pressure monitoring and inotrope support. This is not the case with routine injectable field anesthesia and blood pressures are not expected to be low. Monitoring blood pressure is not possible in the field. Cardiovascular problems may be encountered however when significant overdoses due to lack of training or mathematical errors are given.

**Duration**
Field surgical times should be kept to a short duration (< 35–45 min) to ensure that recovery is more predictable and stable and overall anesthesia risks are minimized. Surgeries requiring a prolonged anesthesia time (> 45 minutes) typically require multiple doses of injectable agents or triple drip mixtures. As the number of additional boluses of injectable drugs increases and the duration is prolonged, the recovery risk of the horse also increases. This is due to the fact that redistribution sites become saturated and the plasma level of the injectable drugs impacts recovery negatively.

Prolonged surgeries in horses should be performed in a facility that can provide additional monitoring and support of cardiorespiratory function. If the option to refer is not possible, the owner should at least be aware of the added risks in an unsupported environment even if the horse is healthy. Owners should also be aware that anesthesia of compromised horses can be a major challenge and should ideally be performed in a clinic with supportive facilities.

**Injury**
Horses are unique and typically respond to stressors with flight/fright avoidance. Their breed and personality alone may influence your anesthetic approach. Other factors to consider are the ability to handle the horse and available assistance. There is always a chance of injury to the handler and horse and the veterinarian must always read the individual horse, situation, and location of induction/recovery.

Once in recumbency, careful attention should be given to protecting pressure points over the shoulders, hips and cheek muscles of the horse. Padding or towels can be placed under the horse’s head to prevent pressure points and protect the lower eye. The upper eye should be covered to prevent excessive light stimulation and avoid trauma. The head should be in a normal relaxed position, and not appear overly extended once towels and support have been placed. Leaving the halter is ideal. If the halter is being left on the horse for control, then the rings and hooks of the halter should be covered and wrapped with a towel, especially on the down side. The lower front leg should be stretched forward with the upper front limb relaxed in a normal position. Hind limbs should be left together without any flexion or extension to aid in proper placement as the horse rolls sternal.

**Withholding Food**
Various opinions exist on feed withholding times in horses. Water should never be withheld in horses to minimize subclinical dehydration and minimize the risk of impactions. Commonly cited times to withhold food for the adult horse are 8–12 hours. This usually refers to inhalational anesthesia but has been extrapolated to the field. Evidence points towards shorter fasting times of 2–4 hours in horses because withholding food >8 hours can contribute to a greater reduction in GI motility. The advantages of withholding food are related to minimizing stomach and abdominal fill to minimize compression of the
diaphragm by the abdomen to decrease V/Q mismatching and improve oxygenation. Withholding food for more than 12 hours is not beneficial to GI motility.

For the field situation if the veterinarian is arriving to perform injectable anesthesia at 8 am, then large amounts of grain and hay should not be fed just before arrival. Feeding small amounts of hay (¼–½ flake) is acceptable in the field or even referral situation especially when anesthesia and surgery are delayed to later in the day. Many horses are kept on pasture and anesthetized by the veterinarian upon arrival.

Excessive feed material in the horses’ mouth should be removed to prevent the chance of aspirating these contents. Horses do not vomit. Concerns of refluxing material with excessive salivation do not exist in routine cases. Remember though to ensure horses are adequately awake after heavy sedation or field anesthesia prior to feeding after surgery. Most agents used (alpha2-agonists) reduce GI and esophageal motility so esophageal impactions have been reported after equine sedation or anesthesia. You should wait a minimum of 1 hour after sedation or field anesthesia prior to feeding.

**Concurrent Medications**

Antibiotics should not be given 30 minutes prior to anesthesia in horses as hypotension has been reported. Although hypotension is not expected to be a concern in field anesthesia with injectable techniques, scientific evidence to confirm antibiotics are safe with field techniques are not available. Caution is therefore advised. Dewormer administration has also been associated with hypotension when administered close to anesthesia. Although this complication is cited when dewormers are given with inhalational anesthetics, the potential exists with field injectable agents as well. Administration of dewormers should occur after recovery from anesthesia when maximal sedative effects have waned and swallowing is strong.

**Drug Options for Field Anesthesia**

The most commonly used field injectable regimes include an alpha2-agonist for premedication, typically xylazine, followed by ketamine with or without diazepam.

**Preanesthetic Sedation**

**Alpha2-agonists**

The α2-agonists produce consistent reliable sedation, decrease the MAC of inhalant anesthetics, reduce the dose of injectable anesthetics, provide analgesia, cause an initial hypertension followed by a decrease in blood pressure to pre-sedation values or lower, decrease cardiac output (by approximately 30%), increase systemic vascular resistance, and decrease heart rate (by approximately 20–35%). Bradyrhythmias (first and second degree atrioventricular heart block) are common after sedation, but transient. Respiratory depression is noted, however, hypoxemia does not commonly develop on its own with standing sedation in horses, even if the horse has small airway disease. Alpha2-agonists increase urine volumes, and decrease gastrointestinal motility.

With maximal sedation, the horse’s head will lower and the horse will be ataxic. Ataxia is dose related and is more severe with detomidine vs. xylazine and romifidine. The lowered head causes the balance of the horse to shift to the front legs and allow them to be able to kick readily with the rear legs when touched abruptly behind the withers. This appears most common with xylazine or romifidine sedation. Raising the horses head can help prevent this sudden kicking.

Providing adequate sedation before field anesthesia in a horse is critical to achieve a smooth induction with muscle relaxation. It is the single most important factor for producing safe uneventful induction of anesthesia and optimizing surgical time. Intravenous administration via the jugular vein will provide the best and most rapid sedation. Although these drugs cause very reliable sedation, an extremely anxious or excited animal with high levels of sympathetic catecholamines, will have a better
Sedative effect with drug combinations such as xylazine and butorphanol. However, these sedative combinations make the horse more ataxic. Some sedatives can also be administered intramuscularly or orally, however the dose will have to be increased to have the same desired effect. In a very excitable, nasty or ‘idiotic’ horse an IM or oral dose may be your only option. Disadvantages and the variability in response may be increased. Dosing IM will require 2–3X the IV dose to achieve the same effect and will take 15–30 minutes for peak effect. An IM dose may assist you to attain IV access for supplemental sedation or administration of the induction agent. Oral administration of detomidine can produce sedation if the drug is absorbed buccally. The drug will not be effective if swallowed. A dose of 60 μg/kg detomidine parenteral formulation can be used, or the oral Dormosedan gel application can be used as directed.

Likely the most commonly used preanesthetic α2-agonist in Canada and the US is xylazine; however detomidine and romifidine can be used. Choice is based typically on cost, preference, availability, and comfort with the drug. High end doses of alpha2-agonists will be necessary to give maximal sedation for field anesthesia.

Maximal doses are as follows:
- Xylazine 1–1.5 mg/kg, IV; 2 mg/kg, IM
- Detomidine 10–20 μg/kg, IV; 20–40 μg/kg, IM
- Romifidine 80–120 μg/kg, IV; 160–200 μg/kg, IM

Lowering these doses will reduce surgical times, induction reliability and smoothness with ketamine. Classically maximal sedation with xylazine at 1 mg/kg occurs between 3–5 minutes. Maximal sedation with detomidine, even IV, is 10–15 minutes.

For field anesthesia, detomidine has a longer duration of action compared to xylazine. This may be a disadvantage due to the longer duration of cardiopulmonary depression, and greater degree of ataxia at recovery. Romifidine may be used in place of xylazine, however research has proven that romifidine as a preanesthetic in horses alone results in more twitching compared to xylazine and diazepam should always be added with ketamine. Mixtures of detomidine and xylazine or romifidine are unnecessary routinely to gain sedation.

Unintentional overdose of αα2-agonists:
It is not uncommon for any veterinarian at any level of their career to unintentionally administer an inappropriate dose of drug, or draw the volume of one intended drug from the wrong bottle. Both situations can result in significant overdosing. With αα2-agonists this situation can be critical when more potent drugs such as detomidine or medetomidine are given. Cases of horses receiving up to 100 mg of detomidine have been reported. With significant overdose, horses are extremely ataxic to recumbent, somnolent, unresponsive, bradycardic, with pale mucous membranes and labored breathing. Reversal with an αα3-antagonist (tolazoline, yohimbine, atipamezole) is necessary. However, access to these drugs may not always be possible quickly. Tolazoline is the only antagonist licensed for use in the horse (2–6 mg/kg, slow IV!); however, it is frequently on backorder. Both tolazoline and yohimbine have less specific receptor antagonist effects, working at both αα1 and αα2. Atipamezole is the most specific antagonist available on the veterinary market. It is not licensed for use in horses. Although a sole large animal practitioner may not carry it, a local small animal practitioner should be contacted in this situation. Atipamezole doses of 0.05–0.1 mg/kg to as high as 0.3 mg/kg have been cited in the equine literature. In emergency situations, IV doses make most sense, however, for equine reversal the lowered doses with slow titration, IV is recommended. Attention to resedation, and gastrointestinal motility are important for 12–24 hours following such high doses.
Supplemental Sedation with Opioids or Phenothiazines

Alpha₂-agonists can be combined with phenothiazines or opioids. Some horses will benefit from the anxiolysis effect acepromazine (0.03–0.05 mg/kg, IV) 20–30 minutes prior to the α₂-agonist and induction. If administered together, the full effect of acepromazine will not be present. Acepromazine may add to cardiovascular depression (hypotension, respiratory depression) and is not an analgesic. It will also promote penile prolapse, which may be problematic in an adult male during induction or recovery. Opioids are frequently combined with the α₂-agonists as preanesthetics to supplement sedation. The most common opioid used in practice is butorphanol; however, morphine can also be used when added sedation and analgesia are required. Disadvantages of the opioid addition are added ataxia. Butorphanol combinations also promote walking/leaning forward on induction compared to sole α₂-agonist preanesthetic sedation. Both require recording of drug use due to scheduling. The added cost of butorphanol currently is ≈ $8.40/ml. Minimal reports using morphine for field anesthesia in horses are available. Typical doses are butorphanol: 0.02–0.05 mg/kg IV; 0.05–0.1 mg/kg IM and morphine: 0.1–0.15 mg/kg IV (slow; but not likely practical in the field); 0.1–0.25 mg/kg IM.

INDUCTION

Benzodiazepines

Benzodiazepines are widely used in equine anesthesia, but in combination with ketamine for induction of anesthesia. They have minimal to no adverse cardiorespiratory effects. They are not used on their own as sedatives due to the fact they cause muscle relaxation and ataxia which will be problematic in an open uncontrolled area in practice. In addition, benzodiazepines do not cause consistent effective sedation in adult horses, even if they are sick. They are effective sedatives in the neonatal foal (< 1 month of age) and the ataxia/recumbency created can be controlled.

Diazepam and midazolam are available for clinical use. Diazepam is not water-soluble and IM absorption is unpredictable. Midazolam is water-soluble allowing for IM absorption; however, only foals will benefit from IM doses on their own.

Doses used with ketamine in adult horses:
- Diazepam: 0.02–0.05 mg/kg, IV
- Midazolam: 0.02–0.05 mg/kg, IV

Doses used alone in neonatal foals:
- Diazepam or Midazolam: 0.02–0.1 mg/kg

Guaiphenesin

Guaiphenesin is used with induction regimes to promote muscle relaxation. It precipitates at room temperature and causes hemolysis in horses at concentrations >10%. It also irritating and should always be administered through in intravenous catheter. Perivascular administration may cause tissue sloughing. It does not have anesthetic properties on its own so should only be used with other induction agents. The degree of muscle relaxation produced is high and quite dramatic making the ataxic horse hard to control in an open environment. It could be used for stall inductions, but will require additional personnel to push the horse against the wall as it is given IV to effect.

Due to all of these factors it is uncommonly used for induction for field anesthesia. In the field, it may be used as part of a maintenance regime with xylazine and ketamine commonly referred to as ‘triple drip.’

Doses necessary as part of induction regimes with ketamine (not typical for the field):
Guaiphenesin: 30–50 ml/kg
**Ketamine**

Ketamine is a dissociative anesthetic that causes anesthesia by interrupting the flow of information from the unconscious to the conscious parts of the brain. The first report of ketamine use in horses was in 1977 and since then it has become the most commonly used injectable agent. Ketamine inductions with or without diazepam have a smoother fall with predictable recoveries and manageable ataxia. Ketamine is never given on its own to horses as it causes excitement, so the effects seen in the horse after ketamine are related to the combined effects with sedative agents. Ketamine alone increases heart rate, cardiac output and arterial blood pressure. These cardiovascular effects will offset the negative cardiovascular effects of the $\alpha_2$-agonist, which is advantageous. Once ketamine is administered, studies have shown that heart rate increases by 16% (still lower than presedation), and cardiac output remains reduced with slight improvement. Surgical stimulation would be expected to improve cardiac output. Ketamine also causes bronchodilation and has minimal effects on gastrointestinal motility.

An apneustic respiratory pattern characterized by a pause following several inspirations is common. Skeletal muscle movement and varying degrees of hypertonus may occur, but these are usually minimized by adequate $\alpha_2$-agonist sedation and or diazepam administration with ketamine. Adequate preanesthetic sedation is essential to ensure the typical lowered dose of ketamine (2 mg/kg, IV) work and to minimize excitatory ketamine effects seen at higher doses. If inadequate sedation is achieved than higher doses of ketamine will be necessary to induce and maintain recumbency, which may impact anesthetic and recovery quality. Once ketamine is administered to the horse, it may take 30 seconds to 1 minute before the horse becomes recumbent. This is due to the prolonged circulation time produced by the reduction in heart rate and cardiac output from the alpha$_2$-agonist premedication. It is important for the practitioner to remember this to allow appropriate timing for elevating the horses head and pushing/pulling back. If this is done too early the horse will object and/or inadvertently fall in an undesirable distant location.

**Ketamine Doses for Induction**
- > 4-month old horses: 2–2.5 mg/kg, IV
- Ponies: 3 mg/kg, IV
- Foals 2 months–4 months: 3 mg/kg

**Alfaxalone**

Alfaxalone has been used for field castrations in 17 ponies (169 kg) sedated with romifidine (100 $\mu$g/kg) and butorphanol (0.05 mg/kg). All horses induced satisfactorily, with stable cardiorespiratory parameters, although blood gases were not measured. Sixty percent of the horses required additional alfaxalone (0.2 mg/kg boluses) for surgery at least once. All recovered acceptably.

**Doses for Induction**

Alfaxalone: 1 mg/kg, IV with sedation

**Thiopental**

Thiopental is the only barbiturate used in the horse. Thiopental is infrequently used for induction in horses currently and use has been replaced by ketamine. Disadvantages compared to ketamine include cardiorespiratory depression (hypotension, reduced myocardial contractility), less controlled induction, rough recovery, and greater ataxia at recovery. These effects are even more significant when sedation and dose reduction are not used. Due to these disadvantages the use of thiopental is not recommended.

**Doses for Induction**

Thiopental: 3–5 mg/kg, IV with sedation
Analygesia, Maintenance and Monitoring with Short-Term Injectable Regimes
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INTRODUCTION
Injectable anesthesia is typically performed on healthy horses for short durations. An injectable protocol must provide an adequate plane of anesthesia and analgesia to facilitate field surgery. The advantages of the standard alpha₂-agonist and ketamine field anesthetic regime include a smooth, more reliable, induction and recovery with good cardiorespiratory stability compared to earlier equine anesthetics. Disadvantages include shorter surgical time attained with a single bolus and potentially poorer muscle relaxation. It is not uncommon for horses to become light during surgery. It is important for practitioners to be able to monitor anesthetic depth appropriately in the field, administer supplemental injectable doses and analgesics as necessary without impacting the cardiorespiratory or recovery stability of standard injectable regimes.

CARDIORESPIRATORY PARAMETERS WITH TYPICAL FIELD ANESTHESIA & SURGERY
Instrumented research horses sedated with high dose xylazine and detomidine have a decrease in heart rate from 35 to approximately 24–25 beats/minute. A similar or even greater decline in heart rate is expected when client-owned horse is sedate. The drop in heart rate will be less when the horse has been dramatically excited prior to sedation or when minimal sedation is attained. The heart rate will be lowest with calm, mature, fit horses. Bradycardia/bradycardias (first and second degree atrioventricular heart block will occur after sedation, but these arrhythmias tend to be transient. In unsedated research horses, mean arterial blood pressure prior to sedation is 120 mm Hg (which is high), and decreases to 90–110 mm Hg when sedated with xylazine or detomidine by 45 minutes. With detomidine IV, blood pressure does increase further for the first 5–10 minutes and then declines; however, a hypertensive phase was not noted with xylazine IV. Based on this, xylazine and detomidine sedation on its own does not necessarily cause hypotension.

Respiratory rate decreases with xylazine and detomidine sedation, but significant decreases in PaO₂ are not evident when standing. Horses may develop upper-airway noises once the head is low with maximal sedation. This will be most pronounced with xylazine and detomidine compared to romifidine. With the head down, it may make it easier for the horse to kick and may also promote upper-airway obstruction secondary to nasal tissue relaxation and edema. Holding the horse’s head up if noises are excessive, as well as when people approach, is recommended.

After induction with ketamine in the alpha₂-agonist sedated horse, heart rate increases secondary to the sympathetic stimulation with ketamine to approximately 35–45 beats/min. Once surgery begins, heart rates increase further to 45–55 beats/minute. Higher heart rates of 50–58 beats/min are noted with younger horses (< 1.5 years) during field anesthesia and surgery. Arterial blood pressure after ketamine administration increases further. Systolic arterial blood pressure Doppler measurements are approximately 120–140 mm Hg, which increase further with surgical stimulation and additional boluses of injectable anesthetics to a level of 140–160 mm Hg.

Horses will hypoventilate after induction without surgery with RR of 6–8/min. Abrupt compression/slapping of the chest wall, twisting the ear or tongue, or pinching the anus can initiate breathing if apnea develops. With surgery the respiratory rate should increase to 20–30/min. An apneustic respiratory pattern, characterized by holding the inspiratory breath in, followed by several shorter inspirations 'in clusters' and then pauses, is common with field anesthesia in horses. Pulse oximetry can be advantageous to monitor hemoglobin saturation (SpO₂) and approximate PaO₂ in the field. Arterial blood gas analysis shows a dramatic drop in PaO₂ within 5–10 minutes with lateral or dorsal recumbency to as low as 50 mm Hg in most horses. PaCO₂ tends to be increased without surgery
and initial hypoventilation. Once surgery starts, PaCO₂ normalizes. PaCO₂ may even decrease as respiratory rate increases in response to a hypoxic drive to ventilate. This increase in respiratory rate should not be confused with a lightened depth of anesthesia without other signs.

The addition of butorphanol to the field anesthetic regime at doses of 0.04 mg/kg has not been found to add to the degree of hypoventilation or reduction in PaO₂. Hypoxemia was most significant with prolonged recumbency, larger or older horses, and those placed in dorsal recumbency compared to younger or smaller horses. Surgical stimulation improved respiratory rate and depth, which resulted in slight improvement in PaO₂ values, although many horses were still hypoxemic (PaO₂ < 60 mm Hg), and all had relative hypoxemia (PaO₂ < 80 mm Hg) on room air. Once the horse regains consciousness a large sigh can be noted, which likely signifies the horse’s response to reduced PaO₂ and attempt to reopen atelectatic areas of lung.

**Monitoring Depth of Anesthesia**

During field anesthesia and surgery, the depth of anesthesia needs to be monitored with head and eye signs, muscular tone, movement, as well as cardiorespiratory parameters. Dramatic changes in heart rate or respiratory rate do not always occur even when the horse is moving. Peripheral pulses may be difficult to palpate due to the hypertension. The described cardiorespiratory ranges with surgery and anesthesia are expected generalizations, but the practitioner should be able to assess eye and head signs quickly to determine surgical level whenever necessary. The practitioner may be working away from the horse’s head, hence having an assistant, ideally a trained veterinary technician, to monitor depth with eye signs is helpful.

The horse’s eye will rotate ventromedial initially after induction and then to a more ventral and middle location in the orbit. The eye should be moist at all times with some tearing. A vigorous palpebral, with or without spontaneous blinking and even mild slow nystagmus is also typical with field injectable regimes. A palpebral reflex in the horse is performed by gently touching the upper eyelid and eyelashes. Touching the medial and lateral canthus, as is performed in small animals, does not always elicit a blink response in a horse and may blunt the actual palpebral reflex. With a surgical plane of anesthesia the eye will move from a ventral medial to ventral middle location in the orbit. If the horse’s plane of anesthesia is lightening, the eye can begin to rotate up and back within the eye orbit, or dorsal laterally, or it may remain in the ventral position but develop a strong persistent nystagmus with more profuse tearing. The horse will also blink spontaneously and hold their eyelid closed signifying greater muscle tone with lightening. This is usually accompanied by tongue and muzzle movement, as well as slight ear twitching. Leg movement, neck tone, neck twitching, swallowing, as well as tail flicking, all signify signs of excessive surgical stimulation and inadequate anesthetic or analgesic depth. If the eye is still, dry, without a palpebral in addition to a lax tongue, nose and neck and hypoventilation with surgery (respiratory rates < 8/minute), the horse is too deep.

These signs are more important to rely on than an individual heart or respiratory rate.

Changes or an increase in heart rate and respiratory rate may not be associated with a lightened plane of anesthesia. Integrating all signs together with surgical relaxation and response are important to decide if additional supplemental boluses are necessary.

**Prolonging Field Surgical Times**

Despite the common use of these drugs, it is not uncommon for a horse to respond to surgery during field anesthesia. The reason for horses getting light in the field may be related to a prolonged timeframe from sedation and induction to the actual start of surgery, inaccurate dosing from underestimation of the horse’s weight, partial perivascular injection, or individual horse variation. Inadequate anesthesia and movement of the horse is very problematic in the uncontrolled field environment. Therefore, the period between induction and incision should always be as short as possible in the field.
After sedation, placement of an intravenous catheter (18-gauge; 1.88-inch; to 14-gauge 4.86-inch angiocath) is always preferred for induction and maintenance of field anesthesia for safety and complete prevention of perivascular or carotid injections. With younger (3–12 months) or any untrained unmanageable horse, placement of an intravenous catheter may not be possible, even with high-dose \alpha_2-agonist sedative doses. After induction however, placement of a catheter is recommended to maintain anesthesia when necessary. Gaining IV access in a moving horse is quite difficult and may take time that is less than ideal once surgery has started. Jugular catheterization with an 18-gauge 1.88-inch small animal catheter is preferred by this author and can easily be secured with crazy glue after induction. Clipping and complete preparation of the jugular is not necessary in the healthy horse (> 1 month of age) for short-term use. The catheter should be removed once the horse is standing. If the catheter is removed in the recumbent horse with high systemic blood pressures, hemostasis is slow and jugular swelling is likely.

**Field Anesthetic Regime and Maintenance**

Monitoring, as described above, is important to decide if and when additional injectable boluses should be administered. If the practitioner knows they will need to prolong surgery time, pre-administration of the injectable top-up before the horse moves is important. Once the horse is actively moving (i.e., trying to right themselves), high doses of xylazine and ketamine will be required. Therefore, monitoring and preplanning additional drug administration will minimize the overall amount of drug to administer. The plasma level of ketamine required to prevent movement in combination with an \alpha_2-agonist is approximately 1 \mu g/ml. In horses undergoing field-injectable techniques, the plasma level decreases to below this by 12 minutes. Therefore, redosing of ketamine to maintain surgical planes of anesthesia is required before 12 minutes in most horses and thereafter. General doses and guidelines to maintain plasma levels of both xylazine and ketamine have been estimated.

As a general rule, the volumes of \alpha_2-agonist and ketamine administered to provide sedation and induction initially should not be readministered in total again during maintenance in the field. As these volumes are exceeded, saturation of redistribution sites occurs and results in a rougher recovery.

**Field Regime Example 1a**
Xylazine: 1.0 mg/kg*, IV; diazepam: 0.02–0.04 mg/kg, IV with ketamine: 2–2.5 mg/kg, IV

**Field Regime Example 1b**
Romifidine: 100 \mu g/kg*, IV; Diazepam: 0.02–0.04 mg/kg, IV with Ketamine: 2–2.5 mg/kg, IV

*High-dose \alpha_2-agonist sedation doses

Xylazine duration is short, and should always be administered in combination with ketamine. Total anesthesia time is approximately 15-20 minutes; however, the actual surgical time may be much less. Additional surgical time can be obtained by administering supplemental dose of xylazine mixed with ketamine at 16–30% of their initial induction dose IV (0.17–0.3 mg/kg of xylazine with 0.33–0.7 mg/kg of ketamine). These volumes can be given at approximately 5, 10, and 15 minutes of anesthesia to prolong surgical anesthesia to 25–30 minutes. Some horses will not require additional injectable doses so monitoring of depth is important in combination with time. If the practitioner knows they will require 30 minutes surgical time additional boluses will be necessary to maintain plasma levels, but the timing can be altered if the horse appears deep. If the horse becomes light with dramatic movement at any time point, the higher dose of both drugs will be necessary and may reach 50% of their initial induction dose.

Romifidine and ketamine combinations for field anesthesia can be maintained the same as xylazine and ketamine in this author’s experience. Both drugs should be administered together at 16–30% to maintain field anesthesia. There is no evidence that romifidine field anesthesia regimes result in less ataxia and smoother recoveries, despite the theory that this \alpha_2-agonist causes less ataxia in horses.
**Field Regime Example 2**

Detomidine 10–20 µg/kg, IV; diazepam: 0.02–0.04 mg/kg, IV with ketamine: 2–2.5 mg/kg, IV

The elimination half-life of detomidine is approximately 50% longer than xylazine following a single IV bolus making it likely that detomidine will accumulate if it is administered with ketamine during top-ups. Maximal sedation with detomidine is between 10–15 minutes, even when IV, in comparison to maximal sedation of xylazine at 5 minutes. However, signs of sedation acceptable to allow a safe consistent induction with ketamine may occur at 5 minutes. If the practitioner induces the horse at 5 minutes, supplemental doses of detomidine with ketamine to maintain the horse will not be necessary at every time point regardless of dose. If high dose detomidine (20 µg/kg, IV) is used as the preanesthetic sedative additional doses of detomidine may not be necessary during early periods (5 min and 10 min) even if the horse is induced 10 minutes after sedation. Supplemental dose of ketamine at 16–30% of the induction dose can be given alone.

Overall these combinations provide approximately 15 minutes of surgical anesthesia. Heart rates are lower and respiratory rate is lower. Similar quality of anesthesia to that observed with xylazine and ketamine is noted, but greater ataxia with an overall rough recovery may occur especially if multiple additional doses are given.

**ADDITIONAL SUPPLEMENTAL ANESTHETICS OR ANALGESICS**

Benzodiazepines should never be readministered to the horse during maintenance regardless of which alpha-2-agonist is used. Additional doses of benzodiazepine are very likely to negatively impact recovery quality and do not supplement analgesia. Additional doses of butorphanol during maintenance are also not recommended. There is no evidence that butorphanol promotes analgesia enough to reduce the need for additional injectable drug administration. In this author’s opinion, high dose butorphanol (> 0.05 mg/kg) or any dose given at the end of surgery increases ataxia and roughens recovery. Horses tend to knuckle on their hind limbs when butorphanol is given close to the recovery period with injectable or inhalational regimes.

Additional supplemental analgesia techniques for field anesthesia include any local anesthetic technique, such as an intratesticular lidocaine administration. Intratesticular lidocaine should be administered at a dose of 1 mg/kg, or approximately 10–20 ml/testicle. Although most veterinary textbooks cite using higher volumes per testicle, larger volumes may promote testicular hemorrhage and spermatic cord swelling which are not desirable. Regardless of which field-injectable regime is used, placement of a regional local anesthetics technique, whenever possible, is ideal to minimize the need for additional anesthetics and promote analgesia.

Lidocaine is a local anaesthetic commonly used in veterinary medicine. In the past 5–10 years, the systemic use of lidocaine has become popular in veterinary medicine. Specifically in horses, it has been used for inhalational MAC sparing abilities, intrinsic analgesic properties, and treatment of equine postoperative and proximal enteritis-induced ileus. The use of systemic lidocaine (2–3 mg/kg, IV) with short-term, field equine anesthesia has been investigated. This investigation supported the fact that typical reliable recoveries with standard xylazine/ketamine regimes are not compromised with the addition of lidocaine, but there may be greater ataxia. This author uses intravenous lidocaine at a dose of 2 mg/kg given IV over 3 minutes once the horse is induced in a case expected to require a longer surgical time. Higher doses can be used, but the practitioner needs to ensure weight accuracy. If the weight of the horse is overestimated and a 3 mg/kg dose of lidocaine is used, then plasma concentrations can reach levels where side effects occur. Higher plasma lidocaine concentrations are also expected when combined with intratesticular lidocaine administration, so the lowered doses should be used for IV when administered together.

With initial administration of lidocaine IV, the horse’s eye will quiet and appear relaxed in a more middle location with less ventral rotation. This correlates with peak plasma levels of lidocaine and within
an additional 5 minutes eye signs will revert to more typical field anesthetic eye signs, as described above. The palpebral reflex should still remain. Cardiorespiratory parameters, including PaO₂ and PaCO₂ do not change with systemic lidocaine administration.

**RECOVERY**

In general, horses induced with an alpha₂/ketamine experience smooth recoveries. Horses do not require additional sedation for recovery, as is necessary with inhalational anesthesia. With additional supplemental injectable doses to maintain surgery, the recovery phase should be longer and may have more ataxia necessitating assistance at the head and tail. A quiet environment without stimulation is ideal to optimize field recovery of horses. A towel can be placed over the horse’s eye to minimize light and protect the eye from dust, debris and flies.

Based on the location and temperament of the horse, the decision can be made to hold the animal or allow them to stand on their own. Young untrained colts may do better without someone holding onto the lead-rope. If the lead rope is held, ensure there is no tension on the rope when the horse moves into sternal position. All horses will stand better if they remain in lateral recumbency for 20–30 minutes after the end of surgery, then go to and remain in a sternal phase for a minimum of 1 minute prior to attempting to stand. Thoroughbred horses have been shown to stand earlier than quarter horses with xylazine/ketamine anesthesia.

If the horse goes into sternal recumbency in a coordinated calm effort, it is unlikely they still have nystagmus. Horses lying in lateral recumbency will typically have nystagmus as drugs are redistributed and metabolized. A strong nystagmus signifies the horse is not ready to stand. Some practitioners will attempt to hold the horse in lateral recumbency until the nystagmus has stopped; however, some horses may object to this and try and stand earlier than if they were left alone.

Encouraging the horse to stand is not recommended. It usually results in a fall or periods of ataxia if the horse is not ready. If additional supplemental analgesics were not administered to maintain field surgery, 20 minutes have passed from the end of surgery, and the horse does not have nystagmus, they may be encouraged to go to sternal, not to stand. Unfortunately, many horses will miss the sternal phase if they are stimulated. Although recovery injuries (horse and veterinarian) are not as common with field injectable techniques vs. inhalational, they still exist.
Equine Field Anesthesia with Triple Drip Mixtures
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INTRODUCTION
The ability of the equine practitioner to perform surgery, as well as provide additional supplemental injectable anesthetic to an appropriate and safe level, can be problematic in the field. Guaifenesin-alpha2-agonist-ketamine combinations may be used to maintain field anesthesia after a standard field induction technique when a longer surgical time is required. The advantages, disadvantages, limitations and specific considerations for field anesthesia with several triple drip mixtures will be reviewed in this session.

GUAIFENESIN (GG)
Guaifenesin (also known as glyceryl guaiacolate or guaiacol glycerine ether) is a muscle-relaxant drug. It is thought to act on the polysynaptic pathways in the spinal cord. It may cause sedation, but does not cause unconsciousness or analgesia. Hence, using it on its own to increase or supplement anesthetic depth in response to surgery is not appropriate. GG based protocols, commonly called “triple drip,” are used as a maintenance regime in the field to provide a longer period of field anesthesia with additional muscle relaxation.

Guaifenesin (GG) precipitates at room temperature, necessitating warming before and during use. It has been shown to cause hemolysis in horses with infusions at concentrations > 20%. Solutions < 10–15% are recommended for use. It is irritating and should always be administered through an intravenous catheter. Perivascular administration may cause tissue sloughing. GG toxicity is described as extensor rigidity or opisthotonus. This can occur as doses exceed total amounts of 75 g (150–250 ml/kg of 5–10% solutions). The infusion should be stopped immediately in this situation.

In a referral center with added personnel and an induction swing gate, GG can be used as part of the induction regime. In this situation it will minimize the sedative alpha2-agonist dose required, minimize movement with hoisting and positioning on the table, with its added muscle relaxation. However, it is difficult to use in the field with an open area during induction. The degree of muscle relaxation produced is high and quite dramatic, making the ataxic horse and impending fall hard to control in an open environment. It could be used for stall inductions, but will require additional personnel to push the horse against the wall, as it is given IV to effect. Once the horse relaxes, but before they fall, ketamine needs to be administered. If the degree of ataxia is great and the horse falls without the unconscious effects of ketamine, the horse will arouse and attempt to stand. Therefore, the timing of ketamine administration is crucial to prevent any excitement.

Due to all of these factors, it is not recommended as part of induction for field anesthesia. In the field, it is most commonly used as part of a maintenance regime with triple drip. Reports of inducing the horse with triple drip mixtures in the literature describe excitement and a less controlled induction period, even with a swing gate setup. Using triple drip mixtures to induce in an open area in the field is also not recommended. The horse should be routinely induced with alpha2-agonist, and ketamine, with or without a benzodiazepine and butorphanol. Once the horse is induced, the triple drip mixture can be initiated. The typical additives to GG are xylazine and ketamine. Romifidine or detomidine can also be used instead of xylazine. Several recipes exist in the literature based on practitioner preference and experience.

The following mixtures can be used to prolong field anesthesia in horses. The contents of the bag should be adequate to prolong surgery for 45–60 minutes. Administering more than 1 bag will negatively impact the horse’s cardiorespiratory function and recovery quality. Triple drip mixtures should not be used to prolong surgery for longer than 60–90 minutes, especially in the field without
oxygen supplementation. Hypoxemia is a major complication encountered with this technique in the field. Long periods of administration result in rough recoveries and potentially myopathy or serious injuries. Attention and efforts to improve oxygenation and padding with prolonged triple drip infusions for field anesthesia are important to their success.

**NOTE: All mixtures have administration rate guidelines, which should be adjusted as necessary from OFF to RAPID similar to a vaporizer throughout a surgery**

**MONITORING DURING GUAIFENESIN-BASED MIXTURES**

As with other typical field injectable regimes or inhalant anesthesia in horses, each animal will have individual requirements. The appearance of horses anesthetized with guaifenesin-based mixtures is quite different than those under inhalant anesthesia and also differs somewhat from injectable only mixtures. Assessing depth takes experience and eye signs will always be present. Horses should still retain a rapid palpebral, but it may not be as vigorous as with injectable only anesthesia. The eye will tend to rotate to a more central location in the orbit. A low-amplitude nystagmus throughout triple drip maintenance is common and trying to obliterate eye movement or nystagmus will make the horse very deep. Ear, muzzle and tongue twitching can still occur at light planes, but overall the horses appear more relaxed and soft. Swallowing is common with triple drip mixtures. Marked urination is common with triple drip protocols, due to the effects of the alpha2-agonist infusion and resultant marked hyperglycemia and glucosuria. Reported heart rate and blood pressures throughout surgery are similar to intermittent injectable doses of alpha2-agonist and ketamine. However, hypotension has been reported with guaifenesin with induction prior to maintenance with inhalational anesthesia. A decrease in blood pressure with triple drip mixtures in the field is possible with excessive anesthetic depth and more likely than with additional intermittent injectable doses for maintenance. Few papers evaluate arterial blood gases with triple drip infusions on room air as would be done in the field. Respiratory rates
in papers with triple drip mixtures during surgery are less than injectable anesthesia with administration of xylazine/ketamine boluses (15–20 breaths/minute vs. 20–30 breaths/minute).
What Is “Herd Health”?  
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The term “Herd Health” means different things to different people: both producers and veterinarians. Many times producers equate a herd health program with a vaccination program. However, much more goes into preventive herd health programs than just a good vaccination program.

It is most cost effective to personalize each program. Many ranches don’t need every vaccine available, and in some cases recommendations don’t fit the business model of the ranch. I stress to producers that they should not use “cookbook” programs found on the internet. They should consult their veterinarian to tailor the program to their ranch.

Good record keeping is extremely important. Herd records along with management changes and new information will allow the herd health program to be fine-tuned each year.

A key point for producers to understand is that cow-calf herd health problems are not usually from a primary disease issue. Management issues (nutrition, biosecurity, genetic selection, etc.) usually allow a disease to take hold. It is futile to chase a disease problem if the underlying management issues are not also addressed.

Herd health programs can be divided into five parts: nutrition; parasite control; biosecurity; vaccinations; and genetics. While each one is important, for Louisiana producers, they are listed in order of importance. In some parts of the world, parasites fall lower in importance.

**NUTRITION**
If nutrition is optimized, health and production will be also. If it is not optimized, diseases and production losses will be a problem. Poor nutrition (protein, energy, vitamins, minerals) depresses immunity to diseases and interferes with response to vaccination. Disease problems may be subclinical, but they will be there.

For cow-calf ranches, nutrition in the brood cow has a major impact on calf health and performance and ultimately the profitability of the ranch. One year of poor nutrition can have impacts for multiple years. When cows cannot maintain adequate body condition, dystocia problems increase. Thin cows have trouble pushing with enough force to have calves in a timely manner. This leads to more stillborn and weak calves. Weak calves are more likely to die of cold stress and have poorcolostrum intake. Cows that cannot maintain their body condition also produce poor-qualitycolostrum, further compounding failure of passive transfer problems. Failure of passive transfer leads to more disease and death in calves. Any calf that gets sick, even if it recovers, will not ever perform to its genetic potential. Calves that have failure of passive transfer but remain healthy still have decreased performance. Cows that calve thin will either not rebreed or will breed late. And heifers born to thin cows, even when managed with appropriate nutrition, will have decreased reproductive performance when compared to heifers born to cows in good condition. This all adds up to fewer pounds of calf weaned per cow for multiple years and decreased productivity of feeder calves and heifers beyond weaning.

**PARASITE CONTROL**
Good parasite control is essential for good health and productivity, especially in young animals. Controlling parasites increases weaning weights, milk production, and conception rates. Parasites are also immunosuppressive, so overall disease resistance and response to vaccines is decreased in parasitized animals.
**Biosecurity**

I do not know who to credit with this quote, but it is one of my favorites: “Most disease is bought and paid for.” A good biosecurity program will protect a herd from diseases in which there is not a good vaccine available or what’s available is very expensive. It is futile to try to eliminate a disease problem if you are not going to prevent it from coming back into the herd. Biosecurity plans can be challenging and time consuming to develop initially, but they are the cheapest and most effective means of disease control. No disease prevention program will work without biosecurity. There are different levels of risk and therefore biosecurity needs with different management/business models. It is up to the veterinarian to discuss the risks of certain management practices and business models and help producers develop practical biosecurity plans that fit each ranch.

Biosecurity plans do not have to be complicated. Since beef breeding animals are usually housed outdoors, the elements help with disease control. Some simple biosecurity recommendations are a good start: test purchased animals for diseases of concern (BVD, trichomoniasis, etc.); quarantine new arrivals and any animals that are returning from shows or sales; avoid fence line contact with neighboring herds; and purchase breeding stock and embryo recipients from as few sources as possible.

**Vaccinations**

As mentioned before, there is no generic/cookbook vaccination program. Many programs are similar, but each should be tailored to the ranch. Management issues such as disease risk, breeding season, disease history, locale, etc. must all be taken into consideration. A “generic” vaccination program would have to cover all known diseases and be safe to recommend for all herds. The result would be a more costly but less effective vaccination program.

**Genetics**

Genetically selecting animals that are more resistant to diseases would be attractive. This is an area of much interest and research is currently ongoing to investigate the genetics of disease resistance for problems such as respiratory disease and parasites.

Fetal programming and epigenetics are also areas of ongoing research. Fetal (or developmental) programming is the concept that a maternal stimulus or insult at a critical period in fetal development has long-term impacts on offspring. For example, nutritional stress in the 1st and 2nd trimesters of pregnancy can lead to problems with fetal organ development and vascularization/placental development. Epigenetics is the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence. The resulting adverse long-term effects reflect a mismatch between fetal environmental conditions and the conditions that the individual will confront later in life. For example, when calves are born to thin cows, they may later have health and performance issues when placed on full feed in the feed yard. Knowing the implications of our management practices could lead to recommendations on matching cows to their ideal environment and managing feeder and breeding cattle for better performance.
Maximizing Calf Health
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Maximizing calf survivability is crucial to economic success of beef producers. Having healthy calves starts many months before calving season. Proper herd nutrition impacts calf survivability more than any other factor. Proper environment/facilities are also important. If these two factors are under control, herd outbreaks of calf diseases will be minimized.

Calf losses are greatest in the first week of life, and most of these are a direct result of dystocia. Some causes of dystocia, such as fetal malpositioning, are impossible to control. However, other causes of dystocia, such as poor nutrition (under or overfeeding), and poor heifer and bull selection, can be minimized with proper management.

PREVENTION
Nutrition
Underfeeding late gestation cows can have a major impact on calf survivability. First, stillbirths will increase, probably due to failure of the cow to go into labor, or due to prolonged labor. Second, birth weights of calves may decrease, as will calf vigor. The producer may not notice this unless records are maintained of cow body condition scores and calf birth weights and survival. This slight decrease in calf birth weight and vigor increases failure of passive transfer, increases cold stress and hypoglycemia, and decreases disease resistance, all of which decrease calf survivability.

Although overfeeding is less common, it can be as damaging as underfeeding. Excess fat in the vaginal cavity can cause dystocia. Overfeeding of heifers can increase fat in the udder, and impact milk production later in life.

Nutrition also impacts vaccine response due to its impact on the immune system (both humoral and cell-mediated immunity). Cows can only respond to vaccines if they have proper energy, protein and mineral levels in the diet. For example, if a cow isn’t taking in enough protein to maintain her body condition, she can’t make antibodies. Therefore, vaccinating cows to protect calves through colostral transfer of immunity will only work with proper cow nutrition.

Historically, focus has been placed on the influence of nutrition in the third trimester on calf health. A newer focus is the influence of nutrition in early gestation and its impact on placental weight (and subsequent fetal growth), neonatal weight and conformation, and body fat makeup and metabolism. Subsequent growth later in life and long-term reproductive health of calves may be impacted by nutrition in these early stages of gestation in their dams. More recently, evidence suggests that supplementation of protein in beef brood cows effects the growth and reproductive efficiency of the female offspring of these cows.

Failure of Passive Transfer
Many immune system defense mechanisms are lacking or deficient in the neonatal calf. Therefore, intake of high-quality colostrum to provide adequate passive transfer of immunity is an important factor in protecting calves from disease. Besides providing circulating immunoglobulins, colostrum provides local immunity in the gut, WBCs that also contribute to local immunity and stimulate cell-mediated immunity (if fresh), and nutritional elements. Calves that receive colostrum have higher growth rates than calves that don’t receive colostrum, even if those calves don’t become ill. This increase in growth rate carries over even into the feedlot.

Several factors can contribute to failure of passive transfer (FPT). Low immunoglobulin concentrations in colostrum of beef cows are usually a result of poor nutrition. Weak calves and poor udder conformation or a poor environment can all interfere with the calf’s ability to ingest colostrum.
And, even if calves ingest adequate amounts of good quality colostrum at the appropriate time, sometimes they do not absorb the proper amounts of immunoglobulins. Dystocia leading to hypoxia and acidosis is probably most commonly associated with poor absorption. Other causes that are implicated but difficult to prove are placental insufficiency due to fetal oversize and/or poor nutrition in early gestation.

Prevention of FPT in an individual calf involves ensuring at least 100 grams of immunoglobulins is ingested. Two liters of beef or four liters of high-quality dairy colostrum is recommended. High-quality dairy colostrum is hard to find, and should come only from farms on a Johne’s control program. Fresh colostrum is better than frozen. But frozen colostrum is far superior to colostral supplements or replacers. The colostral supplements available at this time are not great substitutes for real colostrum, and do not warrant the purchase cost. Colostrum replacers are better, but should not be considered a substitute for good hygiene and management. They may be a better option if the source of outside colostrum is of unknown disease status.

Prevention of FPT on a herd basis involves providing adequate nutrition, providing an environment that allows the calves to stand and nurse without difficulty, minimizing dystocia, and culling cows with poor udder and teat conformation. It’s important to remember that FPT is not a death sentence. On any one farm, there are going to be a few calves that have FPT, even if these farms are well managed. Disease outbreaks in the calf herd start to arise when the numbers of FPT calves increases (usually poor nutrition). The more FPT calves on a farm, the more likely a calf will become sick with a contagious disease (ex. infectious calf diarrhea). Calves are amplifiers of disease because they shed more organisms than the adults, even if not clinically ill. So one sick calf can be the start of a vicious cycle of disease transmission that spreads throughout the herd.

If a specific infectious organism is identified in a calf disease outbreak, vaccination of the cow a month prepartum to passively protect the calf can be considered. But, since outbreaks are more common at the end of the calving season, vaccination rarely helps prevent disease in the current year, but may help prevent cases the following year.

Sanitation
It’s very important to remember that an adequate passive transfer status of the herd can be overwhelmed by a dirty, contaminated environment. Feed troughs and hay racks should be moved periodically, and placed away from waterers and shelter to discourage congregation of cattle in one area, and subsequently concentration of pathogens. If a disease outbreak occurs in the calves, move pregnant animals to a clean pen and leave sick animals in the already contaminated pen. Healthy calves should not move with pregnant cows, since they may be incubating the disease and risk contaminating another pen. If possible, move healthy calves to a third pen. On large operations, cattle should be segregated in groups according to calf age, so that young calves are not exposed to older calves.

Other Preventive Strategies
Umbilical infections can be a problem in some herds, especially during wet years. Dipping navels with 7% tincture of iodine at birth, as well as controlling cattle movement and congregation as discussed earlier, will help decrease the number of umbilical infections in a herd. Umbilical infections, even mild ones that go unnoticed, can lead to weakening of the body wall and umbilical hernias later. Sometimes “outbreak” of umbilical hernias suspected to be genetic in origin are actually from previous umbilical infections.

Proper heifer development and selection, and bull selection are beyond the scope of this article, but are extremely important in decreasing dystocias, weak calves, and FPT. Heifers should be bred to calve early in the calving season so they can be observed more closely for dystocia. In some years, early
weaning of calves born to heifers (and cows if necessary) may make maintaining proper body condition in these heifers easier as they continue to grow.

If embryo transfer is employed, selection of good embryo recipients is crucial. Heifers should be avoided, as should dairy cattle (mastitis, Johne’s disease, poor udder conformation, etc.). Producers should be encouraged to select proven dams from their own herd as recipients. An alternative is to lease proven cows from other producers. Cows should be leased from farms with BVD and Johne’s control programs in place, as well as other biosecurity measures. Embryo recipients are more likely to have large, overdue calves, so close observation during calving is very important.

Feeding at night, or even in the afternoon, increases the likelihood of daytime calving. On farm lay help and veterinary services are more likely to be available during the day, so dystocia problems and weak calves are more easily handled and treated more promptly.

TREATMENT

First Hours of Life
The earlier “at risk” neonates are identified and treated, the better the prognosis for a healthy and productive life. Any calf that is born following a dystocia, even if it appears normal, should be considered at risk. Many of these calves will look normal for a few hours, but deteriorate quickly, so will need to be watched closely. Immediately following the dystocia, while the cow is still restrained, the cow should be milked (if possible) and the calf bottle or tube fed. This ensures colostrum intake and precludes having to restrain the pair later if the calf has not nursed. It also helps prevent hypothermia and hypoglycemia.

Calves born following dystocia can be depressed due to hypoxia, metabolic acidosis, and/or hypothermia. Calves with mild depression can be warmed and given intravenous sodium bicarbonate inexpensively, and this can greatly improve the chances of survival of these calves. If only mildly hypothermic, heat lamps and hot water bottles may work. However, if severely hypothermic, peripheral perfusion is poor and external warming is not very effective. Therefore, these calves need to be warmed from the inside. Warm oral and intravenous fluids (balanced electrolyte solution with 1.5% dextrose) are best, along with external sources of heat. Correcting for a base deficit of 10 is usually safe. Concentrated sodium bicarbonate (5–8%) can be administered undiluted at a rapid rate through a needle if a catheter for other fluids is not needed. Calves with more severe depression may require oxygen therapy, which will increase the cost of treatment. However, many times a small amount of supportive care early prevents having to do more extensive, prolonged care later.

Hypoglycemia
Hypoglycemia is less of a problem in the first hours of life, and more of a problem later secondary to inadequate nutritional intake, diarrhea, septicemia, etc. If severe, hypoglycemia can mimic meningitis with signs such as miotic pupils, opisthotonus, seizures, etc. Glucose levels can be low with both conditions. If other causes of weakness and neurologic signs have been eliminated (hypothermia, acidosis, severe dehydration), a slow infusion of 0.5 ml/10 lb body weight of 50% dextrose IV can be administered without the need of a catheter. If calves have simple hypoglycemia, they will usually respond to the dextrose by improving. If they do not respond, a CSF tap can be easily performed. If the fluid is grossly abnormal, the prognosis is poor, and the owner can factor this into treatment decisions. If the fluid looks grossly normal, the calf may still have meningitis, but the prognosis is good with treatment. If treatment is continued, these calves must have IV 2.5– 5% dextrose, since the 50% dextrose will cause a rebound hypoglycemia if dextrose isn’t continued. Calves should be weaned form 5% dextrose slowly.
Failure of Passive Transfer
In an individual calf with failure of passive transfer (FPT), the most important problems are decreased growth rates and septicemia. Diagnosis of failure of passive transfer can be made at 24 hours up to about one week of age. One of the cheapest tests is serum protein, which should be > 6.0 g/dl in beef calves. There are now newer whole blood tests that can be run without the need of a centrifuge, which allow for immediate on-farm diagnosis.

The only specific treatment for FPT is a plasma transfusion, or more practically, a whole blood transfusion. Plasma is of questionable benefit in healthy calves for prophylaxis because even with high volumes, immunoglobulin levels don’t reach those of calves that received colostrums. This is further magnified if whole blood is given because of volume limits. However, there are other benefits of plasma or whole blood administration, especially in sick calves. The increase in protein levels helps prevent hypoproteinemia if IV fluids have to be given, and if fresh whole blood is given, benefits of cellular immunity, interferon, and other circulating nonspecific immune factors may benefit the calf. Treatment with antibiotics prophylactically in healthy calves is controversial, and should be considered on a case by case basis.

Neonatal Septicemia
A potential sequella to failure of passive transfer is septicemia. Calves under 7 days of age are at greatest risk. The source of the bacteria can be the umbilicus, the GI tract, or the respiratory tract. Any organ system can be secondarily infected, but the neurologic, musculoskeletal and ophthalmic systems are most likely. General clinical signs of septicemia are depression and reluctance or inability to stand. Anorexia, poor suckle reflex, +/- fever (more often hypothermia) are other general signs. Hypoglycemia may be present. Neurologic signs due to secondary meningitis are opisthotonus, seizures, stiff extremities, nystagmus, and/or miotic pupils. Hypopyon, uveitis, synechia, and conjunctivitis may occur but are not life threatening, only a sign of serious problems. Single or multiple swollen joints, edema around the joints and osteomyelitis may occur. Musculoskeletal infections carry a poor prognosis unless caught early. Lameness in neonatal calves should be treated as an emergency. Infectious arthritis from septicemia is a more likely cause of lameness than injury/trauma. Diarrhea and pneumonia are not a common sequella to septicemia in beef calves, although they are common problems in calves with FPT.

A diagnosis of the causative organism(s) requires blood culture. The most likely organism is \textit{E. coli}, but \textit{Salmonella}, \textit{A. pyogenes} and \textit{Staphylococcus aureus} can be involved. Broad-spectrum antibiotics are needed unless a culture and sensitivity shows otherwise. Antimicrobial selection should be based on historical data. Antiinflammatory drugs are also important. If caught early, arthritis can be successfully treated with joint flushes and intraarticular antibiotics. Extensive fibrin buildup will be present in chronic cases that will hinder flushing. Fluid therapy may also be needed.

Umbilical Infections
If an umbilicus becomes infected, and the calf is systemically ill or has poor growth, the umbilicus should usually be immediately removed surgically. Systemic antibiotics rarely work, and the longer the infected umbilicus stays, the higher the risk of the infection spreading to the joints, nervous system, etc. Unlike simple hernia repair, which can be done under sedation and local anesthesia, removal of an infected umbilicus can be more complicated, and general anesthesia is recommended. The surgeon should be prepared to resect infected or abscessed umbilical veins and arteries, and the urachus.
Is Anthelmintic Resistance a Cow-Calf Issue?
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Overview of the Issue
The key word in the title of this presentation is “control.” Eliminating parasites is nearly impossible in most cases and trying to do so can lead to anthelmintic resistance. The goal in controlling parasites is to minimize the economic impacts while allowing some exposure for immunity to develop and minimizing resistance.

What are the impacts of internal parasites? It’s estimated that internal parasites cost the U.S. cattle industry $2 billion per year. This does not include the cost of liver flukes, only stomach/intestinal parasites. A heavily parasitized animal can have clinical disease such as weight loss, diarrhea, and even death. But it’s the subclinical effects of parasites that are most costly and why deworming both cows and calves can be cost effective. Contrary to popular belief, parasites actually make cattle eat less, not more, so the most significant effect of parasite infestations is actually loss of appetite. Parasites also interfere with digestion and absorption of what nutrients are consumed. Therefore, both feed intake and feed efficiency are impacted, leading to decreased growth in calves, and decreased milk production and reproduction in cows. Deworming calves alone can add an extra 10–20 pounds per head at weaning. Deworming the dams of those calves can add even more pounds, as milk production increases by 2–5 pounds per head per day. Deworming cows can also increase pregnancy rates. Another major impact of internal parasites is suppression of the immune system potentially increasing susceptibility to other diseases and interfering with vaccine response. The exact economic impact of deworming will vary from ranch to ranch and from year to year. However, research clearly supports the positive impacts of deworming both cows and calves. So, it is not a question of whether or not to deworm, but when and with what product.

Unfortunately, when it comes to the question of “when and with what,” there is no one-size-fits-all answer. Many factors, including climate, pasture type, grazing management, age and immune status of the animal, etc. determine the severity of parasite problems on an individual ranch in a given year. A unique parasite control program should be developed for each herd. To do this, producers need to know some of the biology of stomach worms, including what goes on in the animal and what happens on the pasture. The nutritional resources available to the herd also impact the effects of parasites.

*Ostertagia ostertagi* is the most pathogenic internal parasite in most beef herds in the United States. It causes two types of infestations. Type I ostertagiasis occurs when *Ostertagia* follows the typical life cycle common to most nematode parasites. The adult worms live in the gut of the animal. The adults breed and lay eggs in the gut, which are passed in the manure. Eggs hatch in the manure and develop into infective larvae, which climb up on blades of grass. The larvae are then eaten by grazing cattle. Once in the gut, the larvae mature into adults and produce more eggs, completing the cycle. Each parasite in the gut can produce hundreds of eggs per day, so over time, adults build up in the gut, and invective larvae build up on the pasture. These adult parasites are responsible for most of the subclinical losses in productivity.

Type II ostertagiasis occurs when environmental conditions are not conducive to larvae survival on pasture; summer in the southern states and winter in the northern states. The larvae that are consumed burrow into the gut, but don’t mature because somehow they know their eggs won’t survive on pasture. The larvae continue to accumulate in the gut, and only mature after environmental conditions improve; fall in the southern states and spring in the northern states. The sudden maturation and migration into the gut of high numbers of accumulated larvae produces severe damage to the gut, with subsequent
clinical weight loss and/or diarrhea. Although all cattle can show signs of Type II ostertagiasis, bulls and Brahman influenced cattle are particularly susceptible. It should also be noted that states across the central U.S. may have combinations of a northern and southern pattern.

While Ostertagia is a problem for cows and calves, Cooperia spp. and Haemonchus spp. are potential problems for calves. Most cattle will be immune to Cooperia spp. and Haemonchus spp. by the time they are yearlings. These are warm-season parasites, so large numbers build up in summer months. Historically, these parasites have been considered to be low in pathogenicity except in unusual circumstances; very high numbers associated with some intensive grazing systems, immunosuppressed calves, etc. However, recent changes in anthelmintic susceptibility may be changing this pattern of pathogenicity.

**Anthelmintic Resistance**

Anthelmintic resistance is a demonstrated reduction in the efficacy of an anthelmintic. More specifically a reduction of the % kill of a particular product at a particular dose against a specific parasite species compared to a proven baseline kill. It’s due to changes in the genetic makeup of the parasite that allows it to survive anthelmintic exposure. Parasites that are resistant to a particular anthelmintic have always existed in parasite populations, but at very low numbers when a product is first introduced. This is sometimes called “tolerance.” Use of the anthelmintic puts selection pressure on the parasite population, allowing resistant populations to slowly increase until the product is no longer effective in controlling the negative effects of the parasites. Once clinical failure occurs, or resistance is detected by current testing methods, it is already widespread in the herd.

Selection pressure for resistance is influenced by many factors. It is extremely complicated and requires more research. However, we know that the number of treatments, the pharmacokinetics and pharmacodynamics of the anthelmintic and the biology of the parasite are all involved. Resistance should not be generalized, but should be characterized by looking at a specific parasite species in a specific animal species given a particular product at a particular location.

One of the most important factors contributing to the buildup of resistant parasites in a population is the level of *refugia*. Refugia is the portion of the parasite population that is not selected by drug treatment; worms in refugia have a genetic makeup that make them susceptible to an anthelmintic. The more refugia in a population, the more the resistance genes in a population are diluted, and the more effective the anthelmintic will be. Refugia can be on pasture or in animals. A good example of the importance of refugia is in small ruminants. A common practice for years was to deworm an entire group of sheep or goats and move them to a pasture that was relatively free of parasite larva (rested, used for crops, grazed by other species, etc). The anthelmintic treatment of all animals at once eliminates refugia in the animals and there are no refugia on the “clean” pasture. The only remaining parasites are resistant to the anthelmintic used. Short-term improvements in animal health are seen because of decreased overall numbers of parasites, but when these remaining resistant parasites multiply, the subsequent population is mostly made up of resistant worms. Buildup over time of the resistant worms eventually leads to treatment failures. Current recommendations are to only deworm selected animals, retaining some refugia in the animal population which will subsequently maintain the pasture refugia.

There is increasing concern about resistance of parasites to cattle dewormers. Resistance is often suspected when poor performance or clinical signs of parasitism don’t improve following deworming. This can be caused by several things and should not immediately be interpreted as a failure of the anthelmintic product. First, products have to be properly, stored, dosed and administered. Secondly, Ostertagia, especially Type II, can cause permanent gut damage in some animals, making them appear refractory to deworming. Thirdly, there are reports of decreased effectiveness of some generic dewormers, so the particular product used may be a factor. This is a very complex and serious issue, and
claims of resistance should not be made in haste or with very little evidence to support them. Conversely, if resistance is occurring, it needs to be documented.

Diagnosis of anthelmintic resistance can be difficult. The current tests available do not detect resistance until it is severe. The Fecal Egg Count Reduction Test (FECRT) is very insensitive in cattle and can at times be misleading. The fecundity of the parasite species, fecal water content, within lab variation, temporary sterilization of worms vs. killing, etc. all impact results. There is currently no test for the gene mutations involved in resistance. Test of this nature would be very helpful in diagnosing resistance earlier and with greater accuracy. The current gold standard requires comparing actual worm burdens in treated and control animals at necropsy. This is both expensive and time consuming and few are trained to perform this testing.

At this time, compared to small ruminants and horses, there are much fewer documented cases of resistance in cattle. Documented cases of resistance to Ostertagia ostertagi, which causes the majority of both clinical and subclinical disease in cattle in the U.S, are rare. Anthelmintic resistance in Cooperia spp. has been documented in the United States, mostly in stocker operations. Cooperia spp. are not usually considered very pathogenic. However, reports of significant disease and economic losses due to Cooperia spp. are increasing as reports of anthelmintic resistance are increasing. It’s been documented that pathogenicity is increased in anthelmintic resistant Haemonchus contortus in small ruminants. This is likely to occur in other parasites of other species, including Cooperia in cattle, but needs further documentation.

At this time, the most concern for the potential to development anthelmintic resistance is with stocker operations. The combination of intensive rotational grazing, young animals, frequent deworming and a parasite that is more likely to develop resistance (Cooperia) leads to the highest potential for the development of resistance. Cow-calf herds should also be monitored, but are much less likely to have problems due to the infrequency of deworming. Of concern for cow calf operations are heifers from stocker operations that were originally destined for the feedyard, that are redirected back to cow-calf operations. If the stocker operation is where resistance is most likely to show up, these heifers could potentially pick up resistant parasites and bring them back to a cow-calf herd. This is one way that multi-resistant parasites in sheep and goats have spread so widely across the country. The constant heavy use of dewormers may have initiated the problem, but animal movements with no consideration of biosecurity and quarantine caused rapid spread of the problem. Another concern is deworming all animals before turnout onto summer grazing in some parts of the country. Deworming the entire herd eliminates refugia in the animals. Pastures that have been unused for months may also have little refugia. So this combination of management practices could have long-term consequences. Turning the cattle out for a month to “seed” the pasture with refugia before deworming might delay the development of resistance, but is not practical in many cases.

**Parasite Control**

The key to parasite control is to deworm often enough and at the right time to minimize the economic impacts while at the same time preventing the development of anthelmintic resistance. This is a tall order and unfortunately we don’t have all the research we need to achieve this balance as of yet.

Except during extremes in weather, for every parasite in the animal there may be thousands of infective larvae on the pasture, so most of the total parasite burden of a ranch is on the pasture. With the introduction of modern cost effective dewormers, the tendency has been to use the products and not think about environmental control, but it’s important that we use a combination of the two.

Parasite burdens are not evenly distributed in a herd. About 20% of animals harbor about 80% of the parasites. In sheep and goats with Haemonchus, the animals with pale mucous membranes are likely those harboring the most parasites. Treating and eventually eliminating only those goats that are pale
will control most of the parasite burden in the animals while leaving some animals untreated maintains refugia. Unfortunately, at this time we do not have a good method to selectively deworm cattle. FECRT could possibly be used in calves, if initial egg counts are high. Leaving some calves untreated will have negative impacts on weight gains. The long-term efficacy of the product must be weighed against the economics of increased gains. FECRT is not a reliable indicator of the level of parasite burdens in individual adult cows.

Historically we have exploited those times of extreme heat or cold when *Ostertagia* larva cannot survive on pasture and most of the total parasite burden is in the animal as hypobiotic larvae. Deworming at this “strategic” time with products effective against inhibited larval stages can greatly decrease the overall parasite burden in a herd. However, it is a very effective way of eliminating refugia and may lead to resistance problems long term.

As mentioned previously, deworming recommendations should be tailored to the locale in the US, and the particular management of the ranch, especially management of grazing and young stock. Knowing the biology of the parasites in the region of the US and how management on a given ranch will impact this biology is essential to developing recommendations. Again, the goal is to decrease the economic impact of parasites while retaining some refugia. Pay attention to biosecurity so resistant parasites are not brought in with herd additions.

Make sure products are used properly. Use only products that are still in date and that have been stored properly and do not underdose. Pick the right product for the right situation. Avoid pour-ons unless external parasites are also a problem. Do not use pour-on dewormers just to control external parasites. “Rotation” of dewormers does not prevent resistance, and in small ruminants and horses, where frequent rotational deworming is used, “rotation” may lead to resistance to many products at once. The infrequent use of dewormers in most cow-calf herds makes rotation less of an issue.

Pasture rotation can theoretically control parasites, but the timing is highly variable depending on stocking density, age of cattle, time of year, recent rainfall, etc. So predicting this from ranch to ranch, year to year is almost impossible. Rotate pastures to maximize nutrition and pasture use, not to control parasites. Maximizing nutrition will secondarily combat the effects of parasites. Co-grazing cattle with other livestock species is another method of combating parasites without using dewormers. In general, cattle, sheep/goats, and horses all have their own separate parasites, and do not infect each other (sheep and goats do share parasites). When a horse, for example, is out grazing with cattle, the horse is eating the cattle parasite larvae. The larvae do not harm the horse, and they do not develop into adults that lay eggs. So the life cycle is broken and there are less larvae to infect the cattle. The horse essentially acts as a vacuum cleaner for the cattle parasites and vice versa.
Preparing Cow-Calf Ranches for Natural Disasters (Lessons Learned from Hurricane Katrina and Friends)
Christine B. Navarre, DVM, MS, DACVIM (LA)
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In the fall of 2005, hurricanes Katrina and Rita were devastating to the Gulf Coast beef and dairy industries. In disasters of this magnitude, it is impossible to prevent all of the devastating losses. But whether it’s flooding, fire, a hazardous material spill, or some other disaster, advanced planning can help veterinarians and producers minimize the loss of animal lives and the health problems associated with disasters. Three years later when hurricanes Gustav and Ike hit the gulf coast, that advanced planning proved invaluable.

Plans should be made for mass evacuation of animals if warning of a disaster is given, and for dealing with rescue, treatment and feeding of animals following a disaster. Cattle, particularly beef cattle, pose special problems when it comes to mass evacuation, so plans should be made well in advance. Veterinarians are considered first responders, and should coordinate plans with other local agriculture related groups such as county extension services, USDA’s Natural Resource Conservation Services and Farm Service Agencies, local cattlemen’s associations, livestock auction markets, feed stores, etc. Different tasks such as livestock hauling; feed, fuel and generator acquisition and distribution; and animal evacuation, rescue and treatment should be assigned to individuals or groups in advance. Primary and contingent holding areas for evacuated and/or rescued cattle as well as staging areas for feed and fuel distribution should be identified in advance. Producers should partner with other farms to provide evacuation space, so other public holding areas can be used for rescued animals. Producers should have safe, efficient penning and loading facilities ready in advance. If flooding or high winds are expected and animals cannot be evacuated, they should be left in large open pastures, and not put in barns.

It’s also important for agricultural groups to coordinate with the local offices of emergency preparedness. These organizations should be made aware of livestock evacuation plans so evacuation routes can be planned. Police and sheriff’s deputies need to know who is authorized to enter areas that might be closed to the public for animal rescue operations. Following a disaster, many rescue organizations will offer help with animal rescue. However, due to the potential dangers of handling stressed cattle, only experienced persons should be involved directly in rescue operations.

Cooperation with state and federal veterinarians and state veterinary associations is a must to prepare for disasters that cover a wide area and involve multiple counties. It is prudent for veterinarians and other key agricultural leaders to have special training in the National Incident Management System. Setting up “central command” with phone banks and volunteers specifically for cattle related problems might be of benefit. Distribution of supplies and prioritization of rescue operations will be facilitated if all calls go through one place.

Well in advance of a potential disaster situation, veterinarians should help producers evaluate their herd health programs. Cattle that undergo evacuation either before or after a disaster will be stressed and are likely to be commingled with other cattle. Herd biosecurity will be breeched, which makes increasing herd immunity imperative. Increased numbers of respiratory disease cases and abortions should be anticipated, and can be minimized with proper herd nutrition and vaccination. In addition, dairy herds are susceptible to increased mastitis problems due to interruption of normal milking schedules. One of the major problems for dairy producers following hurricane Katrina was prolonged power outages. Although most dairies had generators available, many were old and failed
after several days of constant use. Fuel availability was also a problem. Having relatively new, well maintained generators and temporary sources of fuel will help minimize these problems.

Animal identification is also important. If cattle get evacuated and commingled, or escape and are later captured, it’s essential to be able to identify the herd of origin through brands or tags. Individual animal identification will help owners evaluate which animals may be lost from the herd. Veterinarians should be aware of evacuation plans so health papers can be provided in situations such as hurricanes, where advanced warning is given. In some situations it may not be possible to evacuate or rescue all animals, so producers should prioritize animals so their most valuable stock gets attention first. Copies of herd records and registration papers should be stored in a safe place.

Veterinarians should maintain adequate supplies of emergency pharmaceuticals suitable to treat injured or diseased cattle. In large-scale disasters involving high numbers of cattle, providing food and fresh water is the first priority. If animals do need treatment, working facilities should be inspected before use as they may have been damaged. Access to portable working facilities should be arranged in advance. Stress induced respiratory disease outbreaks should be anticipated. Also, damage to chemical storage buildings and fences may allow cattle access to toxic chemicals or plants. Finally, severely injured animals may require euthanasia. Use of barbiturates should be limited to situations where the carcass can be properly buried or incinerated. Key personnel should be trained in the use and safety of firearms for euthanasia.

Besides portable working facilities and corrals, other equipment needs should be arranged. Tractors and forklifts to move feed and supplies, trucks and trailers for hauling cattle, and feed and water troughs may be needed. Following widespread flooding, airboats and cowboys on horseback may be able to reach areas where cattle are stranded. Local residents familiar with the area should be dedicated in advance to acting as guides for out-of-town volunteers. Anyone attempting to rescue or provide food and water to animals either by boat or on horseback should realize that the terrain might have been altered, and underwater debris and fences may not be visible and take proper precautions.

The major widespread long-term destruction of communication systems following hurricanes Katrina and Rita posed major problems in getting information to those who needed it. Many areas were out of land and cell phone service for weeks. Without power, radios could not be recharged and soon were useless, and with many roads impassable, information by word of mouth was difficult. Even areas with phone service may experience very high call volumes leading to inability to get emergency calls through. Advanced notice of feed and fuel staging areas and acquisition of satellite phones for key places are imperative. Feed and hardware stores and milk processing plants are good places to post information. For the dairy producers, milk haulers can be valuable resources to distribute and collect information.

Hard copies of brand commission books and disaster recovery information should be stockpiled in a safe area for immediate distribution following a disaster. County extension offices and Red Cross Centers make good distribution points. Remember that with major power outages, web-based information is useless. Important phone numbers should be posted in several safe places. Numbers for emergency services, state and federal veterinarians, other local agricultural groups, volunteer organizations; information about where donations should be routed; and how to handle carcass disposals should be gathered in advance. Veterinarians should be familiar with county animal control regulations, as these may determine the disposition of rescued animals that go unclaimed.

It’s important to remember that when disasters strike, not only are businesses and animals affected, but families and personal property are affected as well. Veterinarians and other first responders may be faced with the difficulty of juggling animal rescue operations with personal property and family issues. A backup “buddy” system should be in place for veterinarians and technicians to provide help in the immediate aftermath of a disaster, but to also provide some relief when rescue and
cleanup operations continue for long periods of time. State veterinary medical associations can help practitioners set up these backup systems. Multiple backups are needed for each veterinarian/practice. Backups that are in the same area are needed for minor emergency situations, and backups in geographically separate areas are needed in case of widespread disasters.

There is no way to prepare for every situation that arises in a disaster. However, veterinarians are well trained to be leaders in the preparation and implementation of plans for minimizing animal suffering and losses following disasters. By working closely with producers and other agricultural leaders, veterinarians can lessen the impact of a disaster on individual producers and the agricultural economy.

**DISASTER READINESS CHECKLIST FOR BEEF PRODUCERS**

- Herd health and vaccinations up-to-date
- Animal identification
- Health papers
- Prioritize herd
- Records stored in safe location
- Evacuation plan
- Cash available for emergency purchases (credit cards may not work)
- Stockpile food and water
- Emergency equipment and first aid supplies stored
- Partner with other producers/farms
- Coordinate plans with other local agricultural groups
Mind Body Medicine for Veterinarians and Applications in Clinical Practice: “Rekindling the Gift”
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INTRODUCTION
The practice of Veterinary Medicine offers a unique and extremely rewarding professional life. It also offers many challenges that can create stress and impact on one’s mental, physical and emotional health. Mind Body Medicine (MBM) is an essential approach to dealing with the stress of being a health care professional in this time. It is being integrated into conventional human medicine in numerous hospitals and medical centers. It is beneficial for veterinarians to now integrate mind body medicine into their veterinary practices in order to be of benefit to their practice, themselves, their family, staff, clients and patients.

This one-day workshop will review the scientific basis of mind body medicine and how you can use it to be of benefit for yourself, your veterinary practice, your staff, clients and patients. Integration of these beneficial techniques into your veterinary practice and daily life may be one of the most important shifts that you can make in your veterinary life. They will influence every thought, decision and action you make each day. The latest neuroscience continues to document the beneficial changes in our brain function and chemistry when we integrate these techniques.

Once one understands the neurochemical implications of stress on yourself and others and how you can change and manage that in your life, both your practice life and personal life can improve. Solutions, exercises and training based on the relaxation response as defined by the Mind/Body Medical Institute at Harvard Medical School will be reviewed.

The concept of compassion fatigue and “burn-out” within the profession has been discussed much more openly and frequently during this past decade. These concepts and mind body medical approaches to these conditions will also be discussed. Techniques of mind/body medicine offer veterinarians opportunities to reflect on, rejuvenate and re-create our careers and lifestyles.

This workshop will be a combination of lectures and experiential exercises that you can integrate into your veterinary practice and life immediately. These are time-tested and scientifically documented processes that help balance our brain chemistry, physical and emotional health and bring greater joy and satisfaction back into our lives.

Scientific Basis of Mind Body Medicine (MBM) Part 1 & 2
Current Challenges and Stressors
The practice of Veterinary Medicine offers a unique and extremely rewarding professional life. Veterinarians have many gifts to offer others. We bring knowledge and compassion into a healing profession that cares for the helpless. The profession also offers many challenges that can create stress and impact on one’s mental, physical and emotional health. The challenges of practicing progressive medicine, staff management, practice management, client relations, and balancing these with other parts of our lives can become overwhelming at times. The experience of “burnout” is a major risk factor for veterinarians involved in the demanding area of patient care. Substance abuse, crisis management and suicide appear to be on the rise as well. Many veterinary associations now offer substance abuse and suicide prevention support. Research in the UK has shown that veterinarians have a suicide rate around four times higher than the general population. Veterinarians reported a higher level of anxiety and depressive symptoms than a non-clinical normative in the UK population.¹ Veterinarians self-reported stress 46 percent of the time in the UK and 36 per cent in New Zealand.²
A variety of reasons have been proposed for the increased risk of suicide in veterinarians including:

- Easy access to drugs and knowledge and means
- Attitudes towards death and euthanasia
- Suicide contagion
- Cognitive and personality factors
- Work-related stressors
- Complaints at work
- Perceived stigma of seeking help for a mental health problem and stoicism
- High levels of anxiety and depressive symptoms

In addition, chronic long-term stress leads to depressed mental states and other physical health changes related suppression of the immune system and subsequent disease. Chronic stress impacts on the hypothalamic pituitary axis, impacting on numerous neurochemicals and hormones including norepinephrine, cortisol, serotonin, dopamine, endorphins etc. Chronic stress can lead to insulin resistance, systemic inflammation, hypertension, visceral adiposity and adverse cardiovascular responses. Chronic stress actually can cause remodeling of the hippocampus and amygdala.

I might add that in the U.S. numerous veterinarians, as well as human physicians, feel that the increased litigious nature of society and malpractice liability has increased the levels of anxiety and depression. In addition, the recent economic downturn along with increased expenses appears to have increased stress levels throughout many health care professions.

These challenges are not limited to the veterinary profession, but are seen in many healing professions. There is increased discussion regarding “compassion fatigue” in many health professions as well.

Burnout is often the undesired endpoint of a career that began with the noblest of intentions. Burnout sufferers begin to feel cynical, depressed, alienated, and negative about their role as a veterinarian. Some veterinarians choose to leave the profession or explore alternative career pathways within the profession. One source of burnout may lie within the personality of the individual who may feel overly responsible for the welfare of others and use unrealistically high measures of personal performance in evaluating themselves. When caregivers suffer disappointment in patient care, they may become emotionally depleted, lose touch with themselves and others, second guess themselves and eventually sink into professional despair. Developing a way to prevent compassion fatigue is a necessary component of professional development according to Chaplain S. Bryant Kendrick, Associate Professor of Internal Medicine and Gerontology at The Bowman Gray School of Medicine. One other perspective on burnout is that it may correlate with professional stagnation as well. Continuing education and training are key to maintain a stimulating career.

**Mind Body Medicine and Health Care**

This session will focus on Mindfulness-Based Stress Reduction, compassion fatigue and various beneficial approaches. There has been a great deal of dialogue on the impact of chronic stress and compassion fatigue in various medical fields including veterinary medicine. Simple scientific techniques that can be incorporated into your daily life based on research from Harvard Medical School and other research centers will be explained and demonstrated.

Mind/body medicine is a rapidly expanding field in human medicine and its applications for veterinarians are just beginning to be explored. In its simplest definition, Mind/body medicine is the use of our mental activity, thoughts and feelings to help prevent and treat various “diseases.” Studies in mind/body medicine document the effects of thoughts on the release of various neurotransmitters and neurohormones and the impact that has on our physical, mental and emotional health. Many ancient
traditions discuss the essential nature of our mind and its impact on our health. What we think directly impacts on our overall health. One key teaching in Buddhism is on training the mind and cultivating loving kindness. In “The Art of Happiness, A Handbook for Living,” the Dalai Lama states “The systematic training of the mind - the cultivation of happiness, the genuine inner transformation by deliberately selecting and focusing on positive mental states and challenging negative mental states - is possible because of the very structure and function of the brain.”

The Mind and Life Institute has held numerous conferences and published numerous books on the health benefits of various mind exercises and meditation. These valuable resources can be found at the website: www.mindandlife.org/.

Dr. Jon Kabat-Zinn has developed a program called Mindfulness-Based Stress Reduction (MBSR) that has been integrated into many hospitals and medical centers. Dr. Richard Davidson from the University of Wisconsin Neuroscience laboratory has documented the benefits of meditation through functional MRIs. Many of their findings on the healing power of meditation are discussed with the Dalai Lama in “The Mind’s Own Physician.”

One essential mind/body exercise to practice in order to manage the challenges of our career is what Dr. Herbert Benson of the Mind/Body Medical Institute at Harvard Medical School calls “The Relaxation Response.” There are two basic steps necessary to elicit the relaxation response. The first is the repetition of a word, sound, prayer, thought, phrase or muscular activity. The second step is the passive return to the repetition when other thoughts intrude. The relaxation response has been found to decrease respiratory rate, heart rate, blood pressure and oxygen consumption. It has been demonstrated to be effective in the treatment of anxiety, hostility, depression, hypertension, insomnia, chronic pain, premenstrual syndrome, infertility and stress. Other stress-reducing exercises will be taught as well.

Dr. Richard Davidson at the U. of Wisconsin Neuroscience Laboratory is investigating and documenting the cutting edge of the neuroscience of contemplative practice on the brain. He has demonstrated significant benefit to students who had no experience in meditation. He found that simply doing 10 minutes a day of meditation for two weeks showed demonstrable and beneficial changes in the brain through functional MRIs. A discussion of these findings can be found through the website www.soundstrue.com under their free seminar on the compassionate brain. In addition, there are videos of Dr. Davidson discussing his research available at these links...Video of Dr. Davidson’s lecture “Implications of Scientific Research on Meditation for Spiritual Care” at the University of Wisconsin-Madison, 2007 and Video of Dr. Davidson’s lecture “Cultivating compassion: Neuroscientific and behavioral approaches.”

He has also found that mindfulness practice behavioral interventions were able to reduce emotional reactivity and be of therapeutic benefit in chronic inflammatory conditions. Numerous studies are now documenting the health benefits of mindfulness-based stress reduction (mbsr). One study documented the beneficial effects of mbsr on medical and premedical students. The paper that the “ability to cope successfully with the enormous stress of medical education may lead to a cascade of consequences at both a personal and professional level.” They found that participation in mbsr effectively 1) reduced self-reported state and trait anxiety; 2) reduced overall psychological distress including depression; and 3) increased empathy levels. I feel that veterinary students and veterinarians can relate to all of these. The stress of veterinary school only seems to increase upon graduation when one learns to work with difficult clients, staff, school loans and integration of a reasonable work/life balance.

Shapiro et al. also state that “the literature is replete with evidence that the stress inherent in health care negatively impacts health care professionals, leading to increased depression, decreased job satisfaction, and psychological distress.” More articles are appearing in veterinary journals also
acknowledging the toll that chronic stress is taking on veterinarians. Shapiro et al. examined the effects of a short-term stress management program, mindfulness-based stress reduction (MBSR), on health care professionals. Their results from this prospective, randomized, controlled pilot study suggest that an 8-week MBSR intervention may be effective for reducing stress and increasing quality of life and self-compassion in health care professionals. A google search shows numerous studies documenting these benefits. Davidson has documented how meditation impacts on neuroplasticity. They also have found that compassion training alters altruism and neural responses to suffering. In Dr. Davidson’s new book, “The Emotional Life of your Brain: How its Unique Patterns Affect the Way You Think, Feel, and Live - and How You Can Change Them,” the neuroscientist describes various mental exercises that you can use to change your brain and how you feel and live. This is another approach that can be easily integrated both into veterinary school curriculum, as well as into continuing education programs.

Further details and an extensive review of the effects of our thoughts on brain mechanisms and neurochemistry are described by Dr. James Austin, Professor Emeritus of Neurology at the University of Colorado, in his comprehensive text “Zen and the Brain.”

Dr. Davidson and The University of Wisconsin have actually established The Center for Investigating Healthy Minds (CIHM). CIHM conducts rigorous interdisciplinary research on healthy qualities of mind, such as kindness, compassion, forgiveness and mindfulness, which can be viewed at this website: http://www.investigatinghealthyminds.org/.

The behavioral traits of kindness, compassion and forgiveness are often what have driven individuals to become veterinarians. Yet, for some veterinarians, somewhere along our journey, these traits have succumbed to the challenges and stresses of our veterinary profession. By integrating and practicing techniques to maintain a healthy mind, we can nourish those qualities within us again. The goal of CIHM is to create a world in which healthy qualities of mind are investigated and valued. My vision is to integrate these into an integrative approach to veterinary medicine.

Meditation and mindfulness-based stress reduction techniques (MBSR) are being integrated into numerous health care professions, as well as major corporations. For example, mindfulness-based meditation has been integrated into Google’s courses for their employees. One of Google’s first computer engineers and now their current Human Resource director, Chade-Meng Tan developed a course and book titled “Search Inside Yourself, the Unexpected Path to Achieving Success, Happiness and World Peace.” The key is mindfulness meditation. This book offers simple techniques that anyone can easily integrate into their lives. It is one of the most popular courses for Google employees. If it is beneficial for Google, I believe these simple techniques can be easily integrated into veterinary training programs as well. They can assist in making veterinary students and veterinarians calmer, more thoughtful, less stressed, and thereby be of more benefit to our patients, clients and staff. Exercises from this book will be introduced throughout this workshop.

The key to rekindling the gift that we as veterinarians brought into this profession is in our thoughts and our mind. Dr. Joel Robertson, a psychopharmacologist, describes the impact of various neurotransmitters, such as acetylcholine, norepinephrine, epinephrine, serotonin and others, on our moods and performance. Through neurochemical evaluations, he offers simple approaches to maximizing our brain efficiency through nutrition, exercise and mental attitudes. By balancing our neurochemistry, we can enhance performance and prevent burnout. These nutritional, exercise and mental approaches will also be discussed.

Mindfulness-based stress reduction and meditation techniques will be an integral part of preventive veterinary medicine based on the One Health concept. One of the keys to quality veterinary medicine is the mental health and inner peace of the veterinarian and their staff. Mind body medicine is one of the keys to a healthy mind and body. This will be recognized more and more in the next decade.
Throughout thirty-five years of clinical experience in veterinary practice, including emergency medicine, creating and managing a number of multiveternarian companion and equine practices, referral practices and being a professor at various veterinary schools and teaching at numerous conferences, I have found certain techniques that have been beneficial in relationships with staff, colleagues, clients and animals.

Throughout this one-day workshop guided experiential practices with various MBM techniques will be taught. The integration of MBM into relationships with staff, colleagues, clients and animals will be discussed. The practical application and integration of these techniques into your daily veterinary practice will be discussed.

**Personal Burnout Prevention Plan**

Chaplain Kendrick recommends developing a personal burnout prevention plan based on the effects that your thoughts have on your actions. It is based on realistic expectations, the ability to differentiate subjective from objective components of reality, appropriate self-love and support from others. Kendrick feels that this stewardship program “facilitates self-preservation and renewal so that you can adapt to the stresses of the modern health care environment without losing the capability of being there for others.”

Often times we waste energy experiencing frustrations based on expectations that exceed what is really possible. We also tend to not experience the moment, always reflecting on the past or worrying about the future. Often there is a tendency to confuse stress with fear, fear of the past, fear of the future. To assist with this, Chaplain Kendrick also suggests simple mindfulness techniques that assist in regaining the ability to be in the present moment. Too frequently we also fall into the trap of basing our self-worth on someone else’s opinion of our professional performance, creating a performance-based self-esteem system. We need to differentiate who we truly are from what we do. Exercises and creative dialogues will assist us in reflecting on where we began our journey as veterinarians to where we have ended up at this particular point in our career.

Twelve approaches to creating a life and career that works better for us will be reviewed. Many of these approaches are based on mind training and mbsr techniques. These include the openness to change, self-responsibility, feeling our feelings, accepting what is, establishing appropriate boundaries, transforming our self-talk, loving ourselves, exploring the power of choice, commitment, surrender, standing in our truth and re-experiencing joy.

Another approach to mind body medicine focuses on sound healing and the latest research on the effects of sound on brain function. Different binaural sound frequencies have been found to quiet the brain, stimulate alpha, beta and theta waves, decrease stress and increase sense of wellbeing. These sound healing techniques can be very beneficial in decreasing stress at the end of the day. Various sound frequencies and music have also been found to be of benefit to dogs. Veterinary neurologist, Dr. Susan Wagner, authored a book, “Through a Dog’s Ear,” on how sound can improve the health and behavior of dogs and created a CD of classical music that has been clinically demonstrated to soothe a dog’s nervous system.

Recent research on the need for quiet, contemplative time in a busy schedule and life and the implications are updated in the Book “Quiet, The Power of Introverts in a World That Cannot Stop Talking.”

In the final session, the integration of MBM into the bigger picture and the future of veterinary practice and One Medicine Theory will be discussed. In a new documentary, “The Living Matrix, New Insights into Our Bodies, Mind and Health,” various scientists and holistic practitioners explain a new perspective on healing based on an intricate web of factors that determine our well-being based on quantum physics of the human energy field, heart coherence and informational healthcare.
In the epilogue of “Search Inside Yourself,” Tan humorously shares on how we can save the world in our free time based on our thoughts and our mind. Loving kindness and compassion are essential to creating a happier, more peaceful world. We, as veterinarians, can play a major role in reintegrating compassion into the world, person by person, animal by animal, clinic by clinic, hospital by hospital, community by community. In a recent conference on creativity and compassion I was asked how I integrated creativity and compassion into my veterinary career. I shared on how I found some of these techniques beneficial in my interactions with patients and clients in a chapter “A Quiet Space with Animals” in the book “Creativity and Compassion.” As an extension of this conference, The Dalai Lama answered questions from honor students at the university regarding what they could do to help the challenging state of the world. He continued to repeat that one of the most important things one can do is developing our own inner peace, compassion and aspiration to be of benefit to all beings. Both the Dalai Lama and Tan reiterate that when inner peace, compassion and aspiration are all strong within each of us, strong compassionate action comes naturally and organically and thereby it is sustainable. One of my passions throughout my veterinary career has been asking myself the question “What is ultimate healing”? That question stimulated my veterinary journey from its foundational basis in conventional medicine, surgery and animal behavior to exploring complementary approaches such as acupuncture, ethnobotanical medicine, chiropractic and other manual therapies, nutrition and nutritional supplements, homeopathy, and the human animal bond.

I realized that all these therapies together offered a comprehensive integrative approach to animal health care. I also realized that another key to ultimate healing is that we, as veterinarians, develop loving kindness and compassion for ourselves, our staff, our families, colleagues, clients and patients.

We, as veterinarians, are in a unique position as caretakers of animal companions that inherently assist in opening the hearts of our clients. I propose that veterinary medicine may be a much broader field than we ever imagined. Perhaps veterinary medicine can be even more expansive and that each animal care location can be a place for expanding compassion in each and every community and thereby be a vehicle for making the world a happier and healthier place. We have the ability to be of so much more benefit to the world by being and expressing loving kindness and compassion in every thought and action we take. This is how the integration of mind body medicine into our veterinary practices and lives can be of immense benefit to the entire world.

The future of veterinary practice continues to evolve. Stress appears to continue to increase in our practices, as well as throughout the world. A new world view of how veterinary medical practice can be of benefit to all beings in our community and society based on the integration of mind body medicine will be discussed. A new concept of how veterinary practices can become centers of compassion in society and be of practical benefit to all, will be shared.

Through these various experiential processes we can begin to manage our challenging profession better, re-create our heart’s desires and create a career and lifestyle where we will enjoy each moment and each day to its fullest. We will then be able to be of the most service and benefit possible to all beings, two-legged, four-legged and winged.

REFERENCES