CONCURRENT SESSION PRESENTATIONS

COMMUNICATION STRATEGIES FOR DERMATOLOGY: MAKING A CLEAR RECOMMENDATION AND IMPROVING CLIENT FOLLOW THROUGH

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The practice of veterinary medicine and even more specifically the practice of dermatology, frequently involves complex diagnostic and therapeutic recommendations. It is not only our role as veterinarians to make those recommendations but to also assure that clients understand them and understand the possible outcomes if they are or are not followed. Making clear recommendations and opening a dialogue around those recommendations affords our clients the opportunity to engage in the decision-making process and voice their concerns regarding their ability to follow through with those plans.

According to medical and social science research conducted across diverse settings and including a wide range of treatment recommendations, approximately half of all U.S. medical patients are not adhering to their doctor's advice. According to a review of sixty-three studies assessing patient adherence, close to 40% of patients take prescribed medication incorrectly or not at all, and almost twice that number fail dietary restrictions and prescribed exercise or continue to engage in health compromising habits such as smoking and abusing alcohol.¹ The authors purport that nonadherence increases practitioner and consumer frustration and can lead to incorrect diagnoses and unnecessary treatment. In addition, when a recommendation requires more complex regimens that require precision, deviations from optimal regimens can exacerbate disease and sometimes can even be fatal.

In veterinary medicine, a study conducted by the American Animal Hospital Association revealed client adherence to recommendations is much lower than that what veterinarians thought. The study looked at estimated levels of adherence by veterinarians in small animal practices. By and large, the veterinarians overestimated what the actual compliance rates were in their practices. The study limited the study of adherence to six target areas: Heartworm testing and preventive, dental prophylaxis, therapeutic diets, senior screenings, canine and feline core vaccines (DHLPP and FVRCP) and preanesthetic testing. For instance, the overall estimate for therapeutic diets was 59% which was four times the actual adherence rate of 31%; Overall estimate for heartworm testing and preventive was 70% and the actual adherence rate was 48%.

Therefore, low adherence to veterinary recommendations presents complex challenges for the veterinarian and practice team. With increasing breakthroughs in veterinary medicine in primary, secondary and tertiary prevention, poor client adherence is a major problem in animal care. Adherence levels can include lack of follow through on the recommendation, incorrect use of the recommendation (i.e., not completing the full course of antibiotics), failure to maintain wellness care, and others.

Although there are a number of factors that influence client adherence rates in veterinary care, enhanced adherence relies heavily on the quality of the interaction between the veterinarian and client. However, in addition to the interaction that takes place between veterinarian and client, there are other interactions that can influence adherence including those between members of the veterinary health care team and between the health care team members and the client.

There are a number of benefits to client adherence – for the animal, the client, the veterinarian, and veterinary practice. For instance, when clients adhere to recommendations for their animal, it can result in improved health for their animals, thereby minimizing the need for urgent visits. It also means that if their animal is healthier, the client and others that interact with the animal will benefit. It also improves client confidence -- feeling good about taking action and caring out recommendations. Thus, the role they

play is crucial. There are other benefits as well. The veterinarian benefits because it is rewarding and can improve confidence in their ability to communicate with clients around recommendations for their animals. In addition, the veterinary practice benefits when clients adhere to recommendations for their animal resulting in more regularly scheduled wellness and preventive care visits.

Recent studies^{2,3} have elucidated the need for clear recommendations and effective communication with veterinary clients. Kanji et al.², documented the importance of making a clear recommendation regarding the need for surgical or dental procedures. Eighty-three client visits were recorded and coded by independent coders. Medical records were reviewed after six months to determine the number of clients that followed through with the recommendations. Thirty percent of clients followed through the recommendation and clients who received a clear recommendation were found to be seven times more likely to follow through than clients who were not given a clear recommendation.

MAKING A CLEAR RECOMMENDATION

What are the components of a clear recommendation? Things to consider when making a recommendation, how complex is the recommendation, what is the duration of time it will be valid, is it readily available, what challenges would you anticipate the client having with it and what other options does the client have available?

Techniques to consider utilizing include "**ask-tell-ask**" and "**chunk and check**". Ask-tell-ask begins with a "check-in" with the client. This check-in allows the veterinarian to determine the client's background knowledge regarding the topic. An example of how to go about the first "ask" is "*tell me about you know about flea allergic dermatitis*" This allows the clinician to gauge where and at what level of detail to focus the delivery of information or "tell" regarding this topic. It may also elucidate any misinformation the client has, allowing the veterinarian to address this during the "tell". As the "tell" is given, e.g. the diagnostic or therapeutic recommendation is made, the clinician should break the "tell" into smaller "chunks" of information interspersed with intermittent check-ins of client understanding. For example,

"Pemphigus is a disease involving an abnormal response of the dog's immune system. In this situation, the dog's immune system treats areas of its own body as foreign or abnormal and attacks it. That can be kind of confusing, how are you doing so far?"

Utilizing this technique the veterinarian can assure the client is gaining an understanding as the information is provided. Note in the previous example the check-in utilizes an open-ended question requiring the client to answer with more than a yes or no answer. It is important to use clear and simple language and avoid the use of too many numbers. In contrast, providing the entire recommendation from pathophysiology of the disease through treatment plan is in many instance overwhelming and clients are unable to remember all of the questions that occur to them in the process of the receiving the recommendation. The final step is to "ask" the client to provide the key points of the recommendation being made. It is common when first attempting the final "ask" to for the clinician to feel awkward or uncomfortable. Keep in mind that xx% of patients leaving a doctors office express the desire to clarify the recommendation provided to them. ref This knowledge combined with communication techniques that allow the clinician to complete the "ask" with more comfort should allow the clinician to complete the task with relative comfort. Communication skills that can be employed include normalization of the complexity or difficulty of the recommendation and the need to confirm adequate delivery of information. For example, "I know I just provided you with a great deal of information and that this disease is a hard one to understand. In fact, most people have a hard time explaining this to others and I know you will have to explain this to your family. Would you mind going over with me what you feel are the key points or directions you have to remember during the next two weeks of treatment. That way I can help you be clear on all the ins and outs of this treatment plan."

ASSESSMENT OF CLIENT BUY-IN AND CONFIDENCE

Other strategies to consider when making diagnostic and treatment recommendations are related to assessing client conviction in the diagnosis and confidence in their ability to carry out the recommendation. When assessing buy-in the clinician might ask the client to evaluate their belief in the diagnosis on a scale of 1 to 10. Questions such as, "I have talked a lot about how his history and symptoms are consistent with a diagnosis of demodicosis, on a scale of 1-10 with one being not sure and 10 being totally confident, how confident are you that demodicosis is the correct diagnosis for Champ?" This allows the attending clinician to gain a more quantifiable insight into the client's feelings regarding the diagnosis. Similarly, after providing the treatment plan the clinician may choose to assess the client's confidence in their ability to carry out the treatment plan. This could be done by utilizing a statement such as, "we have gone through all of the plans for treatment for the next three weeks, some people find this overwhelming, on a scale of 1-10 with 1 being not at all confident and 10 being very confident, how confident are you that you can complete all of Champ's treatments". A response of less than 8 requires the veterinarian to think about what additional information or treatment plan modification might aid the client in rating themselves as an 8 or better on the confidence scale.

Essential engagement skills to enhance adherence:

Establish trust through:

Open-ended inquiry	Inviting the story from the client in a manner that allows the client to tell you in their words what is wrong, why they have brought their animal in, what they have noticed, etc. Open-ended questions invite more than a yes/no response or other one word responses. Examples include: <i>"Tell me about"</i> <i>"What happened next?"</i> <i>"What brings you here today"</i>
• Reflective Listening	Reflective listening is essential in all communication in which we are trying to understand another person. There are three kinds of reflective listening. The most simple form is a short summary and with a rising tone of voice it is both a statement and a question.
• Express Empathy	We can move beyond the understanding of the situation that the client experiences and move into an appreciation of what the experience was like for the client with expressions of empathy. The empathic connection that can take place between people creates a safe environment for the client. The communication of empathy lets the client know that the clinician has heard them at a deep level. The clinician not only understands what the experience was like for the client; the clinician appreciates the meaning of the experience for the client. <i>"I can understand your concerns -particularly because it's something</i>

that you will be giving Roxie every day for the rest of her life.

- Attention to body language
 It is important to be aware of clues that the client may provide to you that may indicate that they are confused, need clarification, are anxious, or experiencing other emotions. These may be apparent in client facial expressions, shift in eye contact, nervous gestures. In addition, your own nonverbal cues can enhance or inhibit the interaction with your clients including eye contact, posture, tone and volume of voice, etc.
- Attention to language and provide literacy sensitive education
 It makes sense to create an atmosphere where no assumptions are made about the level of health literacy on the part of the client. As a rule, it's

about the level of health literacy on the part of the client. As a rule, it's generally helpful to limit the amount of information given to clients at each visit. It's been estimated that less than half of the information provided to clients during each visit is retained.

One very basic yet often forgotten communication strategy is to use very clear and simple language when providing education to clients. This means eliminating jargon that most likely will create confusion and interfere with an effective exchange. When discussing risk, it's helpful to stay away from use of too many numbers that may overwhelm the client.

Address the following:

- Diagnosis or risk, etiology, and prognosis.
- Use visuals when possible
- Assess the client's understanding

This is particularly helpful to emphasize key points.

Providing information (teaching) is not necessarily what leads to client education. Education is not successful until the client has an understanding of what the problem or issue is and learning has taken place. Thus, it's important to assess the client's understanding of the cause of the problem, why it is important to act upon, and what needs to be done. Ask if the client has asked all of the questions s/he wants to. Give permission to ask.

"We talked about a few things now. I'm wondering what questions you have for me?"

Rather than ask "Do you understand?" instead ask, "What will you tell your wife, (husband, partner, roommate, etc.) about this when you get home?" This will allow the client to explain in his or her own words what their understanding is and will allow you to provide clarification as needed.

Collaborate with the client around recommendation and/or treatment planning

•	Emphasize the value	
	of the recommendation	We know that the manner in which the veterinarian makes the recommendation also makes a difference in the adherence level outcome. For instance, does the message about the recommendation carry weight in terms of importance to the client? We've talked about whether the client can understand the words spoken. Equally as valuable is the level of credibility and value that is attached to the recommendation.
•	Enhance conviction	When clients demonstrate low conviction about a recommendation, they are not ready to take action. Thus, the goals need to be more modest and focused on increasing their understanding of the value of taking action. Some appropriate goals for a client with low conviction include:

- Ask permission to provide new information about the importance of the recommendation.
- *Explore the pros and cons* and the options and choices they have.

• *Encourage small steps* towards action (e.g., read more about the condition and recommendation, discuss with family or others, consider a "trial" to test it out, if appropriate).

• *Provide options* Whenever possible, offer the client options. For instance:

"Would you like the medication in pill form or liquid?"

• *Clarify details of the recommendation* There are many factors that will affect the likelihood that the client will adhere that have much to do with the nature

the client will adhere that have much to do with the nature of the recommendation. For instance, how complex is the regimen? Is it medication that has to be given three times per day - with food? Is it an injection that may be difficult for the client to do? Are they willing to come into the practice for assistance? Is the recommendation something that needs to be given to the animal for a long period of time or for a short duration? Is it important to complete the entire regimen?

Clarify the regimen: If possible, include pictures and clear and specific instruction on what needs to be done (i.e., how often a pill must be given, meal requirements, etc.) *Written instructions:* Written instructions (with pictures) can help people

remember what was said during an office visit.

Motivation: Discuss the positive reasons for following the recommendation.

If the regimen includes medication, discuss administering medications as part of a daily routine: Help the client find consistent daily activities that can serve as cues for giving medication to the animal (e.g., breakfast, TV shows, bedtime, brushing teeth, exercise routine, prior to walking the dog, etc.).

Plan ahead for disruptions: Plan in advance with the client for weekends, holidays, vacations, and other disruptions to the regular daily routines that may interfere with the recommendation.

Describe the possibility of side effects: Discuss potential side effects to be reported to you.

• *Provide written action plan* Written instructions that are literacy sensitive can help individuals remember what was said during an office visit. It may also be helpful to

provide the client with supplemental materials that might be helpful (i.e.,

explanation of the illness, if appropriate).

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NOTES



CANINE AND FELINE HEARTWORM DISEASE

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Canine and feline heartworm diagnostic, treatment and prevention strategies have changed during the previous decade. We experienced an unprecedented increase in the numbers and kinds of available medications and diagnostic aids, and also in the capabilities of pet owners to acquire information. This can be both beneficial and detrimental in our efforts to establish and maintain effective strategies for controlling heartworm infections. Pet owners have become more aware of the potential dangers of heartworm infections. Also, available treatment and prevention products have become more effective and convenient to use. However, much misinformation is communicated through electronic mail and web sites dealing with heartworm. The activities of newer avermectins and milbemycins against microfilaria and larval heartworm control. The same can be said for immunologic tests for in clinic use. Discrepancies between microfilaria tests and antigen or antibody test results can lead to confusion about the actual infection status of pets. In the following, I will discuss some of these issues. My purpose is to draw attention to these issues so that veterinarians can better deal with problems that they create.

Diagnostic challenges confronting veterinarians

Wide spread use of macrolide heartworm preventatives such as ivermectin, milbemycin oxime, moxidectin, and selamectin has had a profound effect on the numbers of heartworm-infected dogs seen by veterinarians. Reductions in the number cases of clinical canine heartworm infections is even more dramatic. The excellent efficacies of the medications, together with the convenience of monthly administration has almost eliminated heartworm infection if some areas - or so it seems. With these enhanced efficacies come some additional problems. Failure to administer these medications regularly or at appropriate doses can result in heartworm infections. However, these infections generally involve fewer numbers of worms - sometimes too few worms to detect. Fewer worms also mean an increased possibility of single-sex infections and failure of worms to produce detectable microfilaria. We also now know that the macrolide preventatives will, to varying degrees, reduce or eliminate circulating microfilaria from infected dogs. Consequently, detection of microfilaria no longer can be considered as reliable a means of diagnosis as it once was. Although point-of-care heartworm antigen tests have become increasingly sensitive and rigorously specific, the lower worm burdens likely to occur in infected dogs seen by veterinarians can challenge the capabilities of these tests. Other phenomena such as fluctuating antigen levels and potentially conflicting antigen test results, antibody test results (for feline tests) and microfilaria test results can create diagnostic dilemmas for the veterinarian. Currently marketed antigen tests approach 100% specificity. Specificity can be a more important test attribute than sensitivity, since most of the dogs in any region are negative. A test with limited specificity would result in a significant number of false positive dogs. These dogs would then be treated unnecessarily with an organoarsenical compound. Reduced sensitivity might fail to detect dogs with low worm burdens (false negatives - a possible occurrence anyway). These dogs are less likely than dogs with high worm burdens to develop severe heartworm disease. Research has shown that currently marketed tests do differ somewhat in their sensitivities, particularly in dogs with low worm burdens. However, for reasons explained above, it is perhaps more important for veterinarians to base selection of point-of-care heartworm tests on test attributes other than sensitivity and specificity. Examples of other attributes include 1) need to process single vs. multiple simultaneous samples (batching), 2) ease of conduct of the test (i.e. number of steps, reagents etc.), 3) ease of visualization of results (brightness of line or dot, or liquid color change), 4) time required to conduct the test, 5) cost per test and 6) other diagnostic capabilities of tests (i.e. detection of antibodies or antigens to other disease agents). Most of the immuno-ELISA and immunochromatographic tests that are currently marketed would score well when these criteria are applied to them. An understanding of situations that today's diagnosis and prevention environments can create is essential if veterinarians are to use these excellent products and diagnostic aids to their full potential.

Emerging issues in the treatment of heartworm infections

Heartworm infection can result in potentially serious and sometimes fatal diseases in both dogs and cats. Fortunately, several safe and effective monthly heartworm preventatives have been developed and delivered to the world market in the last 20 years. All major heartworm preventatives belong to the macrocyclic lactone (ML) class of endectocides. Current MLs approved for heartworm prevention in dogs and cats include ivermectin, milbemycin oxime, moxidectin, and selamectin. All approved MLs exert their effects by targeting a group of ligand-gated chloride ion channels (GluCl) unique to invertebrates. The L_3 and L_4 larval stages of *D. immitis* are exceptionally sensitive to the MLs. Recently, it seems that the frequency of lack of heartworm preventative efficacy (LOE) reports for the MLs in dogs has increased. In reality, failure of any of the preventatives to prevent heartworm infection in dogs is extremely rare (estimated to be <0.1 %). It is not currently known whether the increase in LOE reports is the result of improved tests, increased frequency of testing, clinic or client compliance, a combination of these, or some as yet unidentified factor. When highly effective parasiticides seemingly fail, it is temping to attribute the failures, at least in part, to the emergence of a population of resistant parasites. It is universally less popular to attribute the failures to more likely causes such as pet-owner and pet compliance. In attempt to determine the susceptibility of D. immitis mff to the ML class of preventives, we developed an in vitro microfilariae-based assay to compare laboratory strains of D. immitis. Microfilariae (mff) were purified from EDTA-treated whole blood by centrifugation in a mixture of 0.2% saponin in 0.85% sodium chloride and blood containing mff (ratio 1 blood/11 saponin). Purified mff were suspended in Minimum Essential Medium (MEM) containing 5% Fetal Calf Serum and antibiotics. Candidate macrolide was solubilized in propylene glycol at rate of $1,000 \mu g/ml$ as a stock solution. The stock solution was diluted with MEM to yield concentrations of 50, 38, 30, 20, 15, and 10 µg/ml. Microfilariae were added to wells (20-40 per well depending on available mff) of a 48-well tissue culture plate containing 200 µL each of ML at each dilution or MEM only (0 µg/ml). Plates were placed in a tissue culture incubator at 37 C for 24 hours. After 24 hours, plates were examined and viability mff was assessed based on their motility. Results are recorded as numbers of dead mff/total numbers of mff per well. Data are entered into a statistical program (Polo Plus, LeOra Software, Menlo Park, CA) to obtain probit lines for laboratory strains and field isolates of D. immitis. Differences in the probit lines for each of the strains are compared. Several different laboratory strains of *D. immitis* responded similarly in the assay, indicating that it may be useful in evaluating susceptibility of microfilariae to macrocyclic compounds.

For many years the only adulticidal organoarsenical compound available to veterinarians was thiacetarsamide sodium. The approval and marketing of melarsomine dihydochloride led to the eventual disappearance of thiacetarsamide from the marketplace. Melarsomine provides the veterinarian with a product with improved efficacy, safety and ease of administration compared to its predecessor. Melarsomine was introduced with a unique flexible dosing regimen that was correlated to the clinical condition of the heartworm-infected dog. Dogs that are asymptomatic or in the early symptomatic stages of heartworm disease are given a standard two-dose regimen, with 24 hours intervening between each dose. Dogs with late stage heartworm disease (class III disease) or dogs with suggestion of high worm burdens (semi-quantitative antigen tests; historically high worm burdens in an area; radiographic lesions suggesting high worm burden [not always definitive]) can be given a single dose of melarsomine and subsequently released to the owners care and vigilance at home. The dog is returned one month later to receive the standard two-dose regimen. The rationale for the three-dose regimen is that a partial kill of the adult worms following the single treatment (approximately 50%) and the dog's subsequent recuperation prior to the full regimen a month later would impose less stress and potential for serious post-treatment thromboembolic disease. The safety appeal of the flexible dosing regimen has led many veterinarians to adopt this regimen as their only treatment protocol. Although this reasoning seems logical when devising therapeutic adulticidal protocols, veterinarians must also remember that the flexible dosing regimen increases the period of time that dogs must be confined since worms are killed over two treatment periods. In addition, the pet owner must bear the cost of an additional treatment and must be responsible enough to return for all scheduled treatments. The flexible dosing regimen is the treatment of choice of the American Heartworm Society, for reasons mentioned above.

Another inevitable consequence of the improved product performance of melarsomine is increased cost. In this case, it is undeniable that the excellent properties of melarsomine are well worth the increase in price. The cost of melarsomine therapy, particularly in large dogs, has resulted in some hesitation by pet owners in some markets to pursue adulticidal therapy. This and other issues such as how to deal with heartworm-infected geriatric patients, or patients suffering from other terminal conditions, has resulted in veterinarians considering other adulticidal options. The most popular of these options has been the exploitation of the slow adulticidal effects (sometimes call "soft kill") of the macrolide preventatives (i.e. ivermectin, milbemycin oxime, moxidectin and selamectin). These adulticidal properties are best known and characterized for ivermectin/pyrantel pamoate (Heartgard Plus, Merial). For example, if dogs harboring adult worms are given ivermectin using the dose band regimen (minimum target: dose 6 ug/kg) at monthly intervals for 1.5 to two years or more, many (in some cases most) of the heartworms will die during the regimen. Remaining worms appear structurally abnormal and will likely die. The prevailing mantra seems to be "the older the worms, the longer they will require to kill". It is important to note that the adult worms can induce a proliferative endarteritis in the cardiopulmonary vessels in which they are found, and the longer that they are left in those vessels, the more severe that reaction is likely to become. It is also notable that the chronic effects of slow worm death have been the subject of a very limited amount of research. Some research suggests that the "soft kill" approach should not be used in active dogs or dogs with presenting signs of heartworm disease. At this point it seems that the best advice is to recommend the use of melarsomine when adult infections are detected. If the use of the approved adulticide is refused, then the use of macrolide preventatives in heartworm positive dogs might be justified.

I am often asked about the need to remove mff from heartworm infected dogs. In the past several of us have recommended simply placing microfilaremic dogs on prevention. If adult worms were successfully removed, mff will eventually disappear. I now believe that active removal of mff after the use of melarsomine is prudent for two reasons. Persistent presence of mff exposed to heartworm preventives may increase the likelihood of resistance selection over time. Second, the continued presence of mff serves as a source of infection for supportive mosquito vectors. We have encountered a few dogs whose mff persist, even in the face of milbemycin oxime (0.5 mg/kg per os) or high dose ivermectin (50 μ g/kg and higher either per os or by subcutaneous injection). Such microfilariae have been eliminated in some dogs by concurrent use of doxycycline and normally effective microfilaricides.

Feline heartworm infection: Thoughts and Strategies

Although heartworm infection in cats was first reported in 1921, many pet owners and some veterinarians either remain unaware or do not believe that heartworms can cause serious and sometimes fatal disease in cats. Most of us are familiar the potential consequences of heartworm infections in dogs, but we fail to recognize that heartworm in cats differs somewhat from dogs, and that this parasite induces a significantly different clinical response when present in cats. Although the prevalence of heartworm infection in cats has been studied, unique features of feline infections make the true prevalence of feline heartworm difficult if not impossible to assess. A variety of techniques including radiography/angiography, ultrasonography and necropsy, as well as microfilaria, antibody and antigen detection have been used to diagnose and determine prevalence of feline heartworm infection. However, few tests (ultrasonography and antigen detection are possible exceptions) can be used alone to confirm heartworm infections. Most heartworm experts agree that results of published studies indicate that exposure to heartworm infected mosquitoes in cats is surprisingly high, and that the risk of feline heartworm infection remains a concern in many regions of the country.

Most cats infected with heartworm are asymptomatic. However, it is impossible to predict when and under what conditions asymptomatic cats will develop clinical heartworm disease. Cats with clinical heartworm disease present with respiratory signs such as coughing and/or dyspnea, or intermittent vomiting which according to the pet owner is not associated with eating. Some cats also have signs of weight loss and or diarrhea without respiratory signs. Respiratory signs can be similar to those observed with feline asthma. Consequently, feline heartworm disease must be differentiated from other respiratory disease with similar presentations. A small percentage of cats exhibit acute respiratory distress and may die suddenly. This peracute presentation also mimics signs of feline asthma or cardiomyopathy (dyspnea). Many of these cats are clinically normal prior to the acute heartworm-induced event. Recent research provides additional evidence that early death of pulmonary stages of D. immitis may contribute to the pathogenesis of feline heartworm disease. Results also indicate that lesions and signs of disease associated with death of pulmonary stages of D. immitis resemble those of other deseases such as feline asthma or other cause of tracheitis/bronchitis and interstitial lung disease. Drs. Blagburn and Dillon at Auburn University have applied the name "heartworm associated respiratory disease" (HARD) to this unique and important syndrome. The discovery that immature heartworms can cause severe disease and cannot be easily diagnosed is an important finding. Drs. Dillon and Blagburn are also interested in the potential for HARD to exacerbate pulmonary diseases of other etiologies. At present, our only recourse in treating HARD is the application of symptomatic therapy (i.e. oxygen therapy, bronchodilators, or corticosteroids in severe cases). Heartworm prevention in cats remains the best method of dealing with potential HARD and thromboembolic pulmonary disease caused by the death of adult heartworms. Prevention is now much easier to accept and implement, given the availability of broad spectrum topical parasiticides.

Diagnosis of feline heartworm infection is based on history, clinical signs and ancillary diagnostic aids mentioned above. Both antigen and antibody tests are available and approved for use in cats. While detection of adult heartworm antigen in cats can be a confirmation of infection, it is important to remember that the lower worm burdens and increased likelihood of all-male infections in cats make available antigen tests less sensitive. A positive antibody test might result from one of several situations including current adult infection, recently cleared adult infections, ectopic infections, exposed cats on a heartworm preventative, or simply exposure to heartworm from infected mosquitoes. An increasing number of heartworm-infected cats remain antibody test negative. Infected, antibody-negative cats are difficult to explain and are the subject of much current interest. Because infected cats do not commonly demonstrate circulating microfilaria, standard microfilaria detection assays also cannot be used reliably to confirm infections. Studies also indicate that clinical signs do not correlate with positive serological test results, further substantiating the difficulty of diagnosis. Diagnosis of feline heartworm infection remains a challenge that requires multiple approaches including collection of adequate historical information and/or immunological testing, imaging and perhaps additional hematological tests.

It is important to make three points about feline heartworm infections to clients that are indecisive about feline heartworm prophylaxis. First, clients should be told that feline heartworm infections are difficult to diagnose. The points made in the above discussion can be used to support this statement. Second, feline heartworm disease is not easily or safely treated, nor are there approved or safe medications for removal of adult heartworms from cats. Third, and perhaps most important, clients should be informed that there are safe, effective, and approved heartworm preventative medications available for cats. In addition, these medications are also effective against other important internal and external parasites. It is essential that veterinarians inform and instruct pet owners about risks of exposure to heartworm-infected mosquitoes and about the availability of approved preventive medications. In that way, pet owners can make informed decisions concerning the most appropriate course of action for them and their pet.

Wolbachia: What is it and what do you need to know?

Wolbachia are intracellular bacteria that infect numerous species of filarial worms including heartworms. Many contend that these friendly inhabitants (endosymbionts) play a role in the pathogenesis of diseases caused by heartworms and other filarids. Contention is that host immune responses directed at *Wolbachia* can actually go awry and enhance the disease process in heartworm infections. Some also contend that elimination of *Wolbachia* spp. from heartworms may affect the survival of adult heartworms and microfilariae, the ability of microfilariae to infect and develop within mosquito vectors, and may decrease the host's errant immunologic responses when adult worms are killed or die. Another belief is that since dogs and cats do not harbor *Wolbachia*, certain molecules unique to the bacteria may be used as targets for heartworm detection. This would be particularly helpful in the cats where, as describe above, worm burdens are often too low to detect with traditional antigen detection methods. However, before we get too optimistic, the life cycle of these bacteria involves several different stages. Susceptibilities of the different stages to anti-infective agents may vary. Certain of the stages may be refractory to treatment (diagnosis?) because of their ability to enter quiescent or resting states. At present, there appears to be evidence that pretreatment of heartworm infected dogs with doxycycline at the rate of 20 mg/kg per day (10 mg/kg BID, if necessary) for one month prior to administration of melarsomine dihydrochloride may decrease the severity post-treatment thromboembolic and immunopathologic events. Data also suggest that administration of doxycycline (together with a microfilaricide) also can aid in the elimination of microfilariae from heartworm infected dogs and can render microfilariae noninfectious to mosquitoes.

REFERENCES AVAILABLE ON REQUEST.

NOTES



PARASITIC ZOONOSES

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Introduction

Diseases transmissable from animals to humans are termed "Zoonoses". Published surveys indicate that pet owners are scarcely aware of the myriad of zoonotic disease agents that pets can harbor. In fact, few could name a single disease other than rabies. In the following, I will overview important parasitic zoonoses of companion animals. Understanding biological and epidemiological characteristics of important zoonoses is necessary if we are to implement effective control strategies.

Toxocara spp. ("Roundworms")

Roundworms of dogs and/or cats (*Toxocara canis*, *T. cati*) are large (up to 4.5 inches), stout worms that live as adults in the lumen of the small intestine. *T. canis* is the species commonly found in dogs, *T. cati* is restricted as adult worms to cats. Both *T. canis* and *T. cati* usually undergo hepatotrachael migration prior to establishment in the small intestine. In older dogs and cats, a greater number (but not all) of migrating larvae are diverted to extra-intestinal tissues. The period of time from exposure to the parasite until mature worms are present in the intestine varies based on the route of infection. Generally, this period is between 2 and 5 weeks.

T. canis and *T. cati* remain prevalent in pets, based on recent surveys. Once such survey indicated that *T. canis* eggs were present in the feces of almost 15% of 6,458 dogs sampled from shelters in the United States. Although prevalences were reduced somewhat in adult dogs, the survey results indicate that *T. canis* is not restricted to puppies.

T. canis is a common parasite of dogs, regardless of geographic location, because of the potential for infection by several routes. These include embryonated eggs, transplacental transmission, transcolostral transmission (less common for *T. canis*), and by ingestion of transport hosts such as rodents and rabbits. Transplacental transmission accounts largely for the prevalence of *T. canis* in neonatal and juvenile dogs. Although age-associated immunity aids in the expulsion of some *T. canis* adults as dogs age, it is not completely effective in elimination of the parasites.

T. canis is important not only because of its ability to produce primary disease in dogs, but also because of its ability to produce several extra-intestinal disease syndromes known as "larva migrans" in many hosts, including humans. When ingestion of embryonated eggs results in migration and damage to internal organs, the syndrome is referred to as visceral larva migrans (VLM). VLM is observed most often in children less than 3 years of age. Encysted larvae induce nodules in organs such as liver, lungs, kidney and brain. Such infections generally manifest as profound eosinophilia, pneumonitis and hepatomegaly. Serological surveys suggest that exposure rates to *Toxocara* larvae vary from 3% in one US study, to 23% in other studies, depending on the region, socioeconomic group that is tested, and whether the test population resides in urban or rural areas. In older children (generally 3-13 years) the larvae apparently have a more pronounced predilection for the posterior chamber of the eye. The resulting granulomatous retinitis is the hallmark of this second syndrome known as ocular larva migrans (OLM). OLM can result in severe ocular damage and subsequent retinal detachment, loss of vision, and even blindness. Interestingly, OLM can occur in the complete absence of eosinophilia and signs or evidence of VLM. One graphic example of the potential for Toxocara spp. to cause ocular disease was the report in which an Atlanta, GA ophthalmology practice indicated that 37% (41 cases) of retinal diseases in children seen in children during a 18 month period were caused by Toxocara spp.⁵ Although T. cati is thought to be associated less often with human infections, recent research indicates that it too can cause them.

Adult female roundworms are prolific egg producers. For example, females of *T. canis* are estimated to produce between 25,000 and 85,000 eggs per day. Females of *T. cati* are capable of producing between 19,000 and 24, 000 eggs per day. Given these rates of egg production, it is easy to see how environments can eventually harbor large numbers of eggs. Parasite reproductive rates, combined with the resistance of embryonated eggs to adverse environmental conditions, can increase the risk of exposure and infection to both pets and humans. Roundworms infections can be controlled either by strategic deworming with narrow or broad spectrum agents or by repeated monthly administration of available broad spectrum heartworm preventives.

Baylisascaris procyonis ("Raccoon Ascarid")

Baylisascaris procyonis, is a prevalent and important parasite of raccoons. It is also known to infect dogs. However, such reports are rare. Because, infected dogs can pass eggs in their feces, they should be treated (see below) and precautions should be taken to prevent human exposure to environments that infected dogs have been exposed to. *Baylisascaris* is similar in structure and behavior to *Toxocara* spp. dogs and cats. However, it is not its disease consequences in raccoons that are important, but its capability to cause larva migrans in many other hosts. The raccoon has adapted well to encroachments by humans into its habitats. Given the high prevalences of *Baylisascaris* infection in raccoons (68%-82% in surveys in the United States), the raccoon's broad geographic range, and prevalences in urban environments, it is easy to see why *B. procyonis* is the most common and widespread cause of larva migrans in animals. Although larvae of *Baylisascaris* can invade a variety of tissues in man and other animals, including the eye, it is particularly prone to invasion of the central nervous system. The resulting "neural larva migrans" is the most serious of the migrans syndromes in humans or animals. The seriousness of the condition is a factor of rate of growth and size achieved by larvae compared to other ascarids. Documented infections in humans have resulted in severe, sometimes fatal encephalitis.

Baylisascaris is particularly prevalent in young raccoons, resulting in very high fecal egg shedding rates. The high shedding rates, combined with the raccoon's habit of using communal defecation sites ("latrines"), can result in environments with astonishingly high egg numbers. When these contaminated areas occur in close proximity to urban developments, the risk of human infections increases immensely. Veterinarians should discourage clients from feeding raccoons or adopting them as pets. Clients should also be advised of the potential for environmental contamination with eggs, particularly sites such as fallen trees, tree stumps, and woodpiles that might serve as communal latrines. *Baylisascaris procyonis* infections can be treated with a number of parasiticides including, pyrantel pamoate, Drontal Plus (febantel, pyrantel pamoate and praziquantel), milbemycin oxime, and fenbendazole.

Ancylostoma spp. ("Hookworms")

Canine and feline hookworms are small (up to about 0.75 inches) whitish or reddish-brown worms with a hooked anterior end (hence the name). As adults, they reside in the small intestine of dog, cats and rarely humans. *Ancylostoma* spp. include *A. caninum* (the universally distributed canine hookworm), and *A. braziliense* (found in both dogs and cats in the subtropical US). In the survey mentioned above, *A. caninum* eggs were recovered from almost 20% of 6,458 fecal samples from shelter dogs.

Developmental cycles of hookworms include a free living phase in which larvae hatch from eggs and develop through 3 distinct stages. The 3^{rd} environmental larval stage (infective stage) enters the host either by oral ingestion or by skin penetration. Most (but not all) orally ingested larvae establish in the intestine without extraintestinal migration. Those that penetrate the skin follow a vascular/pulmonary migration prior to their establishment in the small intestine. In addition, both prenatal (transplacental) and transmammary modes of transmission can occur. The reservoir for such larvae is somatic as is the case with *T. canis*.

Hookworms may cause dermal disease, pulmonary disease and intestinal disease. The latter is the most common syndrome in the dog. Hemorrhagic enteritis caused by *A. caninum* can be a peracute, life-

threatening disease in young dogs. In these animals, the transmammary route of infection can lead to the establishment of very high worm burdens in neonatal dogs in a short period of time. The remaining species are less significant pathogens, but not always innocuous. *Ancylostoma caninum*, similar to *T. canis*, is a prolific egg producer. It is estimated that mature females of *A. caninum* can produce up to 20,000 eggs per day. This magnitude of fecundity can result in substantial environmental reservoirs of infective larvae in rather short periods of time.

Free-living infective larvae of some *Ancylostoma* spp. may penetrate the skin of humans and migrate subsequently for short periods of time. These dermal wonderings result in reddish, pruritic, serpentine lesions. This condition is referred to as cutaneous larva migrans (CLM) or "creeping eruption". Although less significant than the larva migrans syndromes caused by the roundworms, the cutaneous syndrome caused by the hookworms remains a concern for veterinarians and pet owners. Larvae of *Ancylostoma braziliense* appear to be the most common cause, although cases of CLM caused by *A. caninum* have been documented. Recent evidence suggests that adults of *A. caninum* may also inhabit the intestines of humans. More than 200 such cases of "eosinophilic enteritis" have now been reported in the medical literature. Human infections with adult *A. caninum* can result in both acute and chronic signs. Clinical signs included recurrent abdominal pain, small bowel thickening, eosinophilia, increased levels of IgE and also inflammation of the distal ileum and colon.

As discussed for roundworms, hookworm infections can be controlled either by strategic deworming with narrow spectrum or broad spectrum agents, or by repeated monthly administration of available broad spectrum heartworm preventives.

Dipylidium caninum ("flea tapeworm", cucumber seed tapeworm")

Dipylidium caninum is a common tapeworm of dogs and cats. It is transmitted by consumption of fleas usually during the pet's self-grooming. Human infections with *D. caninum* occur when fleas are inadvertently ingested, usually by small children. Although not usually of pathogenetic significance, infections in children are a cause of considerable alarm and distress among parents and care-givers when proglottids are passed in feces or are found in soiled diapers. Human infections are best prevented by controlling *D. caninum* in dog and cat hosts. Flea control is a must is complete elimination of *D. caninum* is to be expected. Both narrow spectrum, combination products and combination products with heartworm preventive capabilities are available for elimination of both *Dipylidium* and *Echinococcus* (see below).

Echinococcus spp. ("hydatid tapeworms")

Many tapeworms of dogs or cats are of little primary disease importance and present little danger to either humans or domesticated animals (exceptions are Dipylidium and Echinococcus spp.). Echinococcus species (hydatid tapeworms) are important exceptions. Human and animal echinococcosis, acquired through contact with the feces of infected canids or felids, is a potentially serious disease, requiring constant surveillance by knowledgeable, trained personnel. Echinococcus granulosus uses canids as definitive hosts and many omnivores and herbivores as intermediate hosts. Echinococcus *multilocularis* uses canids and felids as definitive hosts and microtine rodents (voles, lemmings, muskrats, water rats) as principal intermediate hosts. Echinococcus granulosus and E. multilocularis undergo complex cycles of development involving the following morphologically distinct stages: (1) the adult tapeworm (2-11 mm) which inhabits the small intestine of the canine or feline definitive host; (2) the egg, which contains the larval tapeworm (oncosphere); and (3) the metacestode, which contains infective protoscolices in either unilocular or multilocular cysts within the intermediate host. The oncosphere is enclosed within a striated wall (embryophore), which renders the eggs similar in appearance to those of Taenia spp. The metacestode (hydatid) is the replicative stage in the life cycle during which the parasite increases its numbers. When fully developed, the hydatid of E. granulosus consists of a single (unilocular) fluid-filled cyst. The cyst wall is a multilaminar structure which gives rise to brood capsules, each containing numerous protoscolices. The hydatid of *E. multilocularis* is alveolar-like and grows by outward budding of the germinative layer. Invasive growth into surrounding tissues forms many adjacent chambers (hence alveolar or multilocular) containing protoscolices. Both *E. granulosus* and *E. multilocularis* are transmitted through predator-prey cycles. In each instance, the carnivore definitive host becomes infected by ingesting the larval metacestode (hydatid containing protoscolices) within the intermediate host. Eggs and disintegrating gravid proglottids, excreted in the definitive host's feces, are dispersed widely in the environment. Intermediate hosts (including humans) ingest eggs and become infected. Oncospheres are liberated in the intermediate host's intestinal tract and are distributed to many extraintestinal sites via the venous and lymphatic systems. Development leads to the formation of a fluid-filled unilocular hydatid (*E. granulosus*) or a multilocular hydatid (*E. multilocularis*) in many organs. The life cycle is completed when the definitive hosts is caused by either the unilocular or multilocular hydatid cyst. In intermediate hosts, cysts of *E. granulosus* are usually found within the liver and lungs. Other less common sites include kidneys, spleen, heart, bones, and CNS. Disease caused by *E. multilocularis* is more serious than that caused by E. granulosus. The infection is progressive and malignant. Most multilocular hydatid cysts locate in the liver, rarely in other organs.

Fecal flotation is not a reliable means of demonstrating *Echinococcus* infections in definitive hosts. The eggs are similar to those of taeniid tapeworms, and they are excreted erratically in feces. Diagnosis of hydatidosis in intermediate hosts such as livestock or wildlife is best accomplished at necropsy of suspect animals. An array of advanced techniques including radiography, computerized tomography, ultrasonography and scintigraphy has been applied to antemortem diagnosis of human infections. Such procedures, augmented by immunologic assays have proved useful in the detection of human infections. Cestocides are available for treatment of both juvenile and adult *Echinococcus* tapeworms in definitive and intermediate hosts. Treatment of infected dogs or cats with effective cestocides is the best means of control in urban environments. As mentioned above for *Dipylidium*, narrow spectrum products , combination products and combination products with heartworm preventive capabilities are available for elimination of *Echinococcus* infections in dogs if they are encountered.

Giardia spp.

Giardia spp. are dimorphic enteric flagellates that infect the intestine a wide range of vertebrate hosts. The genus *Giardia* consists of several valid species that parasitize mammals, birds, and amphibians. *Giardia duodenalis*, the principal species, can be further divided into at least 7 different genotypes. Human infections are usually caused by assemblage A (rarely B). Most *Giardia* infections are specific to hosts that they infect. For example *G. duodenalis* genospecies C & D are common in dogs and are not thought to infect humans. *Giardia duodenalis* genospecies F is thought only to infect cats. At this point humans infections in the United States have not been attributed to either of genospecies C, D, or F.

Giardia stages consist of a flagellated, binucleate trophozoite, and a quadrinucleate cyst. The trophozoite attaches to the surface of epithelial cells in the small intestine; formation of cysts occurs in the ileum, cecum or colon. Like *Cryptosporidium*, cysts of *Giardia* are immediately infective when passed in feces. Infections result from ingestion of cysts in contaminated environments, food, and water.

Although the mechanism(s) of *Giardia*-induced disease remains unknown, evidence suggests that the disease is likely multifactorial involving inhibition of brush border enzymes or other factors such as altered immune responses, nutritional status of the hosts, presence of intercurrent disease agents, and the strain or genotype of *Giardia* involved in the infection. Most infected animals remain asymptomatic, The most common presenting sign in clinically affected animals and humans is small bowel diarrhea. Feces are usually semi-formed, but may be liquid. Blood usually is not present in animal infections. Feces have been described as pale (often gray or light brown), fetid and containing large amounts of fat. Dogs or cats with giardiasis may present with poor body condition, weight loss, and occasional vomiting. It is not unusual to find *Giardia* coincidentally with other gastrointestinal diseases such as inflammatory bowel disease.

Giardiasis is best diagnosed by fecal flotation using zinc sulfate (specific gravity = 1.18-1.20). Centrifugation of the preparation increases the likelihood of recovering cysts. Also, the addition of a

small amount of Lugol's iodine to the slide prior to placement of the coverslip will aid in visualizing the small $(10-12 \mbox{mm})$ cysts. Use of barium sulfate, antidiarrheals or enemas prior to sampling feces may interfere with detection of cysts and should be avoided if possible. Other diagnostic techniques that can be used to recover trophozoites, cysts, or proteins produced by the parasite include direct examination of feces (wet-mount), immunofluorescent procedures, and ELISA. These techniques are either too insensitive (direct examination) or impractical for the practicing veterinarian because of cost, necessary equipment or because of the effort required to conduct the test.

Given that cysts of the different genotypes are not differentiable based on their structure, it is best to be conservative about the potential for human infections with animal genotypes of *Giardia*. Consequently, it is my view that all animals that are positive by fecal examination should be treated. Several options are available for treatment of *Giardia* infections in dogs or cats. Options include fenbendazole (50 mg/kg X 3-5 days), metronidazole (25 mg/kg BID X 5 days [dog]; 10 mg/kg BID X 5 [cat]), Drontal Plus - (Bayer – approved dose for 3-5days), tinidazole (50 mg/kg SID), nitaxoxanide (100 mg BID X 3 [up to 45 lbs]); 200 mg/kg BID X 3 [45-90 lbs]) It is good practice to treat all animals in a household or kennel that have had contact with infected animals. Bathing animals to remove adherent fecal debris can aid in the control of giardiasis. Provide all animals with clean water since contaminated water is a common source of infection for both humans and animals. A commercial vaccine is available to aid in the prevention and control of giardiasis in dogs and cats. Though normally not considered a first line vaccine, vaccination for *Giardia* should be considered for pets in multiple-pet households, kennels or catteries, or in situations in which giardiasis has been a problem. It has also been suggested that the vaccine might augment treatment of giardiasis in certain problem cases.

Cryptosporidium spp.

Cryptosporidium spp. are small, intracellular coccidia-like protozoans that can infect a variety of tissues and organs in vertebrate hosts. Most *Cryptosporidium* spp. that infect mammals undergo development at the luminal end of enterocytes of the small intestine. However, when either medications or diseases such as AIDS alter the hosts immune system, *Cryptosporidium* spp. may spread to less common sites such as the stomach, lung, or ducts associated with the liver or pancreas.

At present, there are 15 recognized species of *Cryptosporidium*. The most important of the valid species are *C. parvum*, a causative agent of cryptosporidiosis in many species of mammals and *C. canis/C. felis* in dogs and cats. *Cryptosporidium parvum* can be further divided into at least 6 different genotypes or cryptic species, based on molecular characterizations and host specificity. It is important to note that at least two genotypes of *C. parvum* and perhaps 6 additional species of *Cryptosporidium* are capable of infecting humans. The developmental cycle of *Cryptosporidium* includes asexual and sexual stages similar to stages in the life cycles of canine and feline coccidia. Similarly, the life cycle of *Cryptosporidium* culminates in the production of resistant oocysts that are shed immediately infective with feces into the infected host's environment. This differs from most other coccidia, which require a period of time to develop to the infective sporulated oocyst. Oocysts of *Cryptosporidium* spp. can remain viable for many months, if protected from extremes of temperature and from dessication. Available data suggest that human cryptosporidiosis results from ingestion of oocysts shed into the environment from other humans, farm animals, companion animals, or by consuming contaminated food, drinking water, or recreational water.

Clinical signs of cryptosporidiosis in animals and humans include diarrhea, abdominal pain, dehydration, and weight loss. Both human and animal cryptosporidiosis are usually self-limiting diseases lasting little more that 2 weeks. However, in hosts with abnormal immune responses (including immunocompromised humans), cryptosporidiosis can be a chronic, life-threatening disease.

Diagnosis of cryptosporidiosis in animal or humans can be confirmed by detection of oocysts or *Cryptosporidium*-specific antigens in feces. Oocysts are small (4-6 \square m) and difficult to visualize using standard fecal flotation procedures. Commercially-available fluorescent antibody kits can aid in visualization of oocysts, but require an epifluorescence microscope. ELISA kits are available for detection of fecal antigens, but they are expensive and require strict adherence to step by step procedures.

At present, the only approved drug for treatment of cryptosporidiosis is nitazoxanide (Alinia[®], Romark Laboratories - 100 mg BID X 3 [up to 45 lbs]); 200 mg/kg BID X 3 [45-90 lbs])). Other agents such as paromomycin (125-165 mg/kg twice daily for 5 days (dog and cat), azithromycin (5-10 mg/kg twice daily for 5-7 days [dog]; 7-15 mg/kg twice daily for 5-7 days [cat] and tylosin (10-15 mg/kg three times daily for 14-21 days) also have been reported to have activity against *Cryptosporidium*.

Toxoplasma gondii

Toxoplasma gondii is a ubiquitous protozoon parasite that infects virtually all warm-blooded vertebrates. It is estimated that up to 33% of humans worldwide possess circulating antibodies to T. Gondii, implying either active infection with the parasite or prior exposure. Three distinct structural stages comprise the life cycle of T. gondii: Sporozoites within infective oocysts, tachyzoites in pseudocysts or groups, and bradyzoites in tissue cysts. Domestic cats and other felids serve as definitive hosts for T. gondii. All remaining hosts, including humans, serve as intermediate hosts. Within intermediate hosts, the parasite replicates as asexual tachyzoites. These stages divide quickly (hence the name), destroying cells and organs in which they develop. Tachyzoites can infect many different cells and organs, which accounts for the multi-systemic nature of the disease. Eventually, tachyzoites transform into slowly dividing bradyzoites and are enclosed by a cyst wall. Bradyzoites remain inactive until they are ingested by definitive hosts. Within the intestinal tract of felids, T. gondii undergoes a typical coccidia-like life cycle which culminates in the production of oocysts that are passaged in feces. The greatest number of oocysts are shed by kittens during their first infection.During these shedding events, millions of oocysts can be passaged during a short patent period of about 2 weeks. It was once believed that after an initial infection and subsequent oocyst shedding, cats remained immune to the parasite and would passage oocyst again. However, recent research indicates that after lapses of several years, it is possible for cats to passage oocysts if tissue cysts are ingested.

Once in the environment, oocysts develop to the infective stage in 1 to 5 days. Sporulated oocysts can remain viable for many months in protected environments such as damp soil. Intermediate hosts (including humans) are infected by ingestion of sporulated oocysts from the environment, or by consumption of raw or undercooked tissues that contains cysts. The tachyzoite is the stage that crosses the maternal fetal interface and infects the developing fetus in utero. Infection by this route is referred to as congenital toxoplasmosis. If infection occurs after birth, usually after ingestion of sporulated oocysts or tissue cysts in raw or undercooked meat, the disease is referred to as acquired toxoplasmosis.

In immunocompetent humans, toxoplasmosis is either an inapparent, asymptomatic infection, or a brief flu-like illness. Persons experiencing the latter usually present with fever, malaise and enlarged, inflamed lymph nodes. Toxoplasmosis can be a severe, life threatening disease in immunocompromised persons, especially those with AIDS. In such cases, resting bradyzoites within tissue cysts in the brain revert to the tachyzoite stage and divide repeatedly. Rapid reproduction of the parasite, unimpeded because of a compromised immune response, results in severe brain disease or toxoplasmic encephalitis.

In about 10% of cases, congenital toxoplasmosis results in abortion or neonatal death. Newborns can also suffer from the classic triad of retinochoroiditis, intracranial calcification, and hydrocephalus. Others develop a complex of symptoms including fever, anemia, convulsions, splenomegaly, hepatomegaly and lymphadenopathy. Those infants that survive infection during the post-natal period can suffer from progressive neurological deficiency. Many of these children require specialized care for the remainder of their lives.

Feline toxoplasmosis, when it occurs, usually results in systemic disease. Symptomatic cats often present with dyspnea, polypnea, icterus, and abdominal discomfort. Ocular disease, characterized by uveitis and retinochoroiditis is also common in cats with systemic toxoplasmosis.

Toxoplasmosis can be prevented by avoiding contact with sporulated oocysts in the environment and avoiding consumption of raw or undercooked meat. This can be achieved by washing hands after exposure to soil, sand, raw meat or unwashed vegetables, cooking or freezing meat thoroughly, avoiding untreated drinking water, and for pregnant women, allowing someone else to change the cat litter tray. Both fecal examination and serological techniques can be used to detect either intestinal infection (oocyst shedding) in cats or systemic infection in cats and other hosts. It is important to remember that cats generally shed detectable oocysts for short periods of time. Negative fecal results only confirm that the cat is not currently shedding oocysts. Shedding could have occurred prior to fecal examination or could occur at some time in the future. Also, cats may be seronegative at the time that they are shedding oocysts. Therefore results of fecal examination and serologic tests must be interpreted with some caution. Positive serologic tests can be helpful in either diagnosing or ruling out systemic toxoplasmosis.

A number of drugs including sulfonamides, clindamycin, and pyrimethamine can be used to treat systemic toxoplasmosis or reduce oocyst shedding in cats.

Prevention of companion animal zoonoses: What pet owners should know.

- 1. Purchase or adopt animals from reputable breeders and shelters that maintain only healthy animals. Animals less that 1 year of age are more likely to be infected with potentially zoonotic agents. However, this is not always the case.
- 2. Establish and maintain regular veterinary visitation schedules (i.e. at least annually) for vaccines, fecal examinations, and wellness examinations. Remember that certain important parasites are not eliminated by broad spectrum parasite control products.
- 3. Use broad spectrum internal parasite control products, particularly those used primarily for heartworm prevention or ectoparasite control that also possess activity against other internal parasites (i.e. *Toxocara* spp., *Ancylostoma*. Spp.)
- 4. Consult with your veterinarian regarding all cases of diarrhea in dogs and cats. Consider seeking medical advice if prolonged diarrhea occurs coincidentally in pets and pet owners. This is particularly important for persons who are immunocompromised.
- 5. Support leash and fecal removal laws and policies in pet exercise areas and public places.
- 6. Feed pets only commercially prepared, complete rations. Do not feed animals raw or undercooked meat, or allow them to hunt and consume prey.
- 7. Avoid feeding wildlife such as raccoons. This behavior encourages their immigration into developed human environments and exposure to potential zoonotic agents.
- 8. Pet owners should discuss concerns about potential zoonoses with veterinarians, physicians, trained parasitologists, or infectious disease and public health experts. They should not presume that all information from sources such as lay publications, the Internet, and email groups is either accurate or up to date.

REFERENCES AVAILABLE ON REQUEST.

NOTES



ANTIMICROBIAL THERAPY: UPDATE ON FLUOROQUINOLONES FOR DERMATOLOGY

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INTRODUCTION

The fluoroquinolone drugs in current use include enrofloxacin (Baytril, Bayer Animal Health) which was the first veterinary fluoroquinolone approved for use in veterinary medicine, orbifloxacin (Orbax, Merck Animal Health), and marbofloxacin (Zeniquin, Pfizer Animal Health). Marbofloxacin has also been registered for small animals in Europe as Marbocyl. Difloxacin (Dicural) is approved for dogs but has not recently been marketed. Ibafloxacin is approved in Europe, but not the U.S. Pradofloxacin (Veraflox) is approved for both dogs and cats. The other fluoroquinolone in common use in the U.S. is ciprofloxacin, which is not approved for animals but is administered, usually to dogs, as the human generic tablet.

What is the role of fluoroquinolones in veterinary dermatology? A review of the properties that pertain to veterinary dermatology was written by this author and other collaborators in 1999 (Ihrke, et al, 1999). Even though several years have passed since that review, the important pharmacology and properties of these drugs has not changed. For the treatment of superficial (superficial bacterial folliculitis) and deep pyoderma in dogs, there is support for clinical efficacy. The evidence was summarized in the 1999 paper cited earlier (Ihrke, et al, 1999). More recently, Summers and colleagues (Summers et al, 2012) examined published clinical papers from studies with marbofloxacin, ibafloxacin, and pradofloxacin. For ibafloxacin and marbofloxacin, the authors concluded that there was "insufficient evidence for/against recommending use of the drug". For pradofloxacin, there was "fair evidence for recommending use of the drug". In addition to published studies, these drugs are approved by regulatory agencies who have concluded that these drugs are safe and effective for skin infections.

EVIDENCE TO SUPPORT PHARMACOLOGIC ACTIVITY FOR SKIN INFECTIONS MIC Data

The minimum inhibitory concentrations (MIC) for wild-type strains of Staphylococcus pseudintermedius isolated from skin infections of dogs are typically in the susceptible range. The veterinary fluoroquinolone breakpoints are from CLSI interpretive criteria established for dogs and cats (CLSI, 2008). The susceptible breakpoint ("S") is 0.5 μ g/mL for enrofloxacin, and $\leq 1.0 \mu$ g/mL for orbifloxacin, marbofloxacin, and ciprofloxacin. A breakpoint has not yet been established for pradofloxacin. The ciprofloxacin breakpoint is from the human standard may not necessarily be accurate for dogs or cats. The typical range of MIC values for a standard strain of *Staphylococcus* used for quality control testing (QC) is 0.03-0.12 µg/mL for enrofloxacin, 0.12-0.5 µg/mL for marbofloxacin, 0.25-2 µg/mL for orbifloxacin, and 0.03-0.12 µg/mL for pradofloxacin (CLSI, 2008). Average MIC values for Staphylococcus pseudintermedius from available literature, including the manufacturer's data, were as follows (Ihrke et al, 1999): enrofloxacin 0.125 µg/mL, marbofloxacin 0.23 µg/mL, orbifloxacin 0.39 µg/mL, and ciprofloxacin 0.25 µg/mL. Differences in MIC values provide a relative comparison of activity among these drugs, but do not translate to differences in clinical efficacy because the MIC values must be compared in relation to achievable blood concentrations. It should be noted that the MIC values for a gram-negative bacilli (Escherichia coli) is considerably less by at least one or two dilutions, which emphasizes the higher activity of this class of antimicrobials against bacteria of the Enterobacteriaceae compared to gram-positive cocci. By contrast, MIC values for typical strains of Pseudomonas aeruginosa are at least 2 to 4 fold higher than for Staphylococcus.

Pharmacokinetic Data

The comparative pharmacokinetics of fluoroquinolones in animals have been published (Heinen, 2002; Bidgood & Papich, 2002; Frazier et al, 2000) and many other studies have been summarized in a book chapter (Papich & Riviere, 2009). Although there is variability among these studies, there is general agreement in the important parameters of peak concentration (C_{MAX}) and area-under-the-curve (AUC) that can be used to predict whether or not the plasma concentrations reach the desired pharmacokinetic-pharmacodynamic (PK-PD) target. The values of C_{MAX} and AUC are derived from plasma concentrations, which should be adjusted for plasma protein binding as only the free (protein unbound) fraction of the drug is considered active. As shown by Bidgood & Papich (2002), the AUC of unbound fluoroquinolones in the interstitial tissue fluid of dogs exceeds the plasma concentration; therefore, the plasma concentration can be used to predict clinical efficacy, but may actually underestimate the concentration in the tissue biophase.

PK-PD Data

To achieve a cure, the drug concentration in plasma should be maintained above the minimum inhibitory concentration (MIC), or some multiple of the MIC, for at least a portion of the dose interval. Antibacterial dosage regimens are based on this assumption, but classes of drugs vary with respect to the peak concentration and the time above the MIC that is needed for a clinical cure. Pharmacokinetic-pharmacodynamic (PK-PD) relationships of antibiotics attempt to explain how these factors can correlate with clinical outcome. There have been several excellent references that have explained the use of these indices for clinical dosing, including the articles by Nicolau et al. (1995), Hyatt et al. (1995), McKellar et al (2004), Craig (1998), Drusano (2007), Mouton, et al, 2005, and Lees & Aliabadi (2002).

Fluoroquinolones are concentration-dependent antimicrobials. Both the peak concentration to MIC ratio (C_{MAX} :MIC), or the area-under-the-curve to MIC ratio (AUC:MIC) have been associated with antibacterial success. As reviewed by Drusano et al (1998) and Wright et al (2000), investigators have shown that either index may predict clinical cure in studies of laboratory animals, and in a limited number human clinical studies. Without clinical studies in animals, PK-PD targets are extrapolated from other species or studies in research animals. Although both the C_{MAX}:MIC or AUC:MIC is associated with successful treatment, if the C_{MAX}:MIC ratio cannot be maximized, the AUC:MIC ratio may be a better index of therapeutic success (Ambrose & Grasela, 2000; Drusano et al 1998). There may be a difference in AUC/MIC ratios between gram-positive and gram-negative organisms. That is, AUC/MIC ratios for successful treatment may be lower for gram-positive bacteria than for gram-negative bacteria. This was shown in the paper by Ambrose & Grasela (2000) and suggested by others (eg, Wright et al, 2000) in which they presented data and reviewed the relevant publications. Most authors cite a AUC:MIC ratio of >100 or >125 as an optimum target for gram negative infections and a ratio of approximately 30-55 for gram-positive infections.

Using the values for MIC cited above, and considering the pharmacokinetic values from studies cited earlier, the administration of the lowest label dose of the currently available fluoroquinolones to small animals usually meets the goal of a C_{MAX} :MIC ratio or a AUC:MIC ratio in the range cited above. Specifically, AUC/MIC at the lowest registered label dose produces a value >100 for gram-negative bacteria (*E. coli*) for marbofloxacin, orbifloxacin, difloxacin, and enrofloxacin (plus metabolite ciprofloxacin) in dogs. The same dose yields a AUC/MIC ratio above 50, but not necessarily above 100 for these drugs against *Staphylococcus*.

To take advantage of the range of dosing for fluoroquinolones, low doses of fluoroquinolones have been administered to treat susceptible organisms with low MIC, such as *E. coli* or *Pasteurella*, or to attain a lower AUC/MIC ratio for gram-positive cocci. An exception to these assumptions is seen with *Pseudomonas aeruginosa* which usually has the highest MIC among susceptible bacteria. The MIC values for *Pseudomonas aeruginosa* are at least 2 to 4 fold higher than for more susceptible bacteria such as *Staphylococcus*. This translates to a need for a high dose to attain the PK-PD target needed for these organisms. Even at these high doses, it may not be possible to reach the PK-PD target necessary for a cure because MIC values for *Pseudomonas aeruginosa aeruginosa* can often be in the resistant range. Bacteria such

as enterococci and anaerobes are more resistant. Even at high doses, a sufficient peak concentration or AUC:MIC ratio will be difficult to achieve for these organisms using currently available veterinary drugs.

ARE FLUOROQUINOLONES "FIRST CHOICE" DRUGS FOR SKIN INFECTIONS?

Published guidelines from various groups have recommended that the fluoroquinolones *should not* be used as first-choice (also called "first tier") therapy for skin infections. These recommendations have been published or in the process of reaching consensus by the British Small Animal Veterinary Association (BSAVA), Federation of European Companion Animal Veterinary Associations (FECAVA), *Association Francaise des Veterinaires pour Animaux de Compagnie* (France) and soon to be published by the International Society of Companion Animal Infectious Diseases (ISCAID). These recommendations have risen from a concern for bacterial resistance, and the recognition that fluoroquinolones are still regarded as an important class of antimicrobials for use in people. It is also recognized that use of fluoroquinolones has been associated with emergence of resistant strains of bacteria, including methicillin-resistant *Staphylococcus* species (Dancer, 2008; Deresinski, 2005; Guardabassi, et al, 2013). In these guidelines, fluoroquinolones are included in the list of second-choice ("second tier") drugs that can be used when first-choice drugs cannot be used.

Despite being listed as "second-tier" drug choices, fluoroquinolones can be valuable in refractory cases, or, as indicated above, when first-choice drugs cannot be used. Unfortunately, they are usually not active against a resistant strain of *Staphylococcus pseudintermedius* (MRSP). The available data indicates that strains of MRSP are usually multi-drug resistant and most are resistant to the fluoroquinolones (Perreten et al, 2010; Frank & Loeffler, 2012).

Accepted indications for a fluoroquinolone are patients that cannot tolerate other drugs for treating susceptible infections. Some patients are sensitive to β -lactam agents either because of allergy or susceptibility to adverse gastrointestinal events. Some animals also may be sensitive to sulfonamides, or to the GI effects of macrolides and lincosamides (eg, clindamycin). In these instances, fluoroquinolones can be acceptable alternatives. Fluoroquinolones also are more lipophilic than the commonly used β -lactam antibiotics. If an infection is located intracellular, the fluoroquinolones – by virtue of their intracellular penetration – may be more effective (Drusano et al, 1998).

PRADOFLOXACIN: ONE OF A NEW GENERATION OF FLUOROQUINOLONES

Of the current, more familiar fluroroquinolones, (eg, enrofloxacin, marbofloxacin, orbifloxacin) there are deficiencies in the spectrum of activity. They have less activity against gram-positive cocci and anaerobic bacteria than gram-negative bacilli. The newest generations of fluoroquinolones (referred to by some authors as the 3rd-generation quinolones, and others as 2nd -generation fluoroquinolones) include gatifloxacin, gemifloxacin, moxifloxacin, and the new veterinary drug pradofloxacin (Veraflox, Bayer Animal Health). These new fluoroquinolones, with substitutions at the C-8 position (C-8 methoxy or C-8 cyano, for example), have a broader spectrum that includes anaerobic bacteria and gram-positive cocci. The difference in spectrum of activity is largely caused by increased activity against the DNA-gyrase of gram-positive bacteria, in addition to its activity against Topoisomerase IV, which is the target in gram-positive bacteria for the older quinolones (Pestova et al, 2000; Hooper, 2000). Premafloxacin is the only other veterinary fluoroquinolone that is also in this group, but it has never been evaluated clinically.

Pradofloxacin (Veraflox) 2.5% oral suspension was approved by the U.S. FDA in November 2012. It has not been approved for dogs in the U.S. but is approved for this species in Europe. For cats, the agency concluded that "The data demonstrate that Veraflox oral suspension, when used according to the label, is safe and effective for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida, Streptococcus canis, Staphylococcus aureus, Staphylococcus felis*, and *Staphylococcus pseudintermedius*." The approved dose of 7.5 mg/kg oral, once a day for 7 days is higher than the approved European dose. (Europe approved dose for cats is 3 mg/kg for tablets and 5 mg/kg for oral liquid suspension.) Pradofloxacin has been safe in cats with respect to ocular lesions (Messias et al, 2008).

Prior to this approval it was evaluated in dogs and cats in research abstracts and clinical reports (Restrepo et al, 2010; Stephan et al, 2008; Spindel et al, 2008; Hartmann et al, 2008; Litster et al, 2007;

Mueller & Stephan, 2007). Pharmacokinetic studies are also available (Hartmann et al, 2008). *In vitro* susceptibility data indicates that it is more active than other fluoroquinolones against bacterial isolates from dogs and cats (Ganiere, et al, 2005; Silley et al, 2007; Stephen et al, 2008; Körber-Irrgang et al, 2012). Because it is active against two targets of fluoroquinolones (Topoisomerase IV and DNA gyrase) *in vitro* development of resistant mutants may be less likely (Wetzstein 2005; Setphan et al, 2007).

For conditions that would be considered "unapproved" in the U.S. it has been effective. At a dose of 3 mg/kg orally it was effective for treatment of urinary tract infections in dogs (Stephan et al, 2004) and at 5 mg/kg was effective for canine pyoderma (Mueller & Stephan, 2007). At a dose of 5 mg/kg in a 2.5% oral suspension it was effective for urinary tract infections in cats (Litster et al, 2007).

CIPROFLOXACIN USE IN ANIMALS

Veterinarians are encouraged to consider veterinary-labeled fluoroquinolones in their patients before human-labeled drugs because safety and efficacy data have been specifically derived for animals before FDA approval. Ciprofloxacin is a human drug, not registered for animals. However, it has been used in the United States by veterinarians because of the flexibility allowed in the extra-label use regulations (AMDUCA). It is illegal to administer to food animals. When used in small animals, the use is considered extra-label and subject to other extra-label restrictions (eg, a veterinarian-client-patient-relationship – VCPR – need to be established).

Since ciprofloxacin became available in a generic formulation, there has been interest in its use in animals because it is less expensive than veterinary formulations and is available in large tablets (for big dogs). It was safe in cats when administered at 100 mg/kg without producing ocular toxicity (Schluter 1987). But, when cats were given ciprofloxacin orally oral absorption is low 22-33% and would not be effective for gram-positive bacteria even at 10 mg/kg (Albarellos et al, 2004). At 10 mg/kg every 12 hours, it was able to reach therapeutic targets against susceptible gram-negative bacteria.

The *in vitro* activity, based on MIC values, is higher for ciprofloxacin than the available veterinary fluoroquinolones (Rubin et al, 2008; Riddle et al, 2000). Despite better *in vitro* activity against some pathogens, one cannot assume that this translates to better efficacy without PK-PD data, and clinical studies. In dogs, oral absorption of ciprofloxacin has been reported in only a few limited studies. Estimates derived from independent studies (Abadía et al, 1994; Abadía et al, 1995; Walker et al 1990), indicates that oral absorption may approach 74 to 97%. However, in a crossover study reported, (Nakamura et al, 1990) the oral absorption in dogs was only 42%. These values are quite different from the fluoroquinolones registered for animals, which have near complete bioavailability. Ciprofloxacin oral absorption in people is approximately 70%.

A new published study in dogs in which generic ciprofloxacin tablets were administered sheds some light on the source of the variability in oral absorption (Papich, 2012). In this study, Ciprofloxacin was administered as a 250 mg generic oral tablet (mean dose 23 mg/kg) and 10 mg/kg intravenous (IV) solution in a crossover study. After blood sample collection and drug analysis, pharmacokinetic analysis was performed using compartmental modeling. Deconvolution analysis was performed by using the unit inpulse response function to evaluate in vivo drug release from absorption data. The terminal half-life (t¹/₂) was 2.6 hr (CV 10.8%), AUC 22.5 µg•hr/mL (CV 62.3%), and systemic absorption (F) 58.4% (CV 45.4%). The oral absorption of these human-label generic tablets was highly variable, with some dogs exhibiting only 30% oral absorption, but others approximately 80% oral absorption. We believe that the variability may be caused by failure of the oral generic tablet to undergo complete dissolution in the canine GI tract because when ciprofloxacin solution was administered orally, the plasma concentrations were more uniform and consistent among dogs with absorption of 71% (CV 7.3%). This study concluded that inconsistent oral absorption of ciprofloxacin in some dogs may be formulation-dependent, and affected by tablet dissolution in the canine small intestine. It is difficult to calculate reliable oral doses for dogs because of this variability. If one calculates a dose using the data for oral tablets in these dogs and a AUC/MIC target ratio of 100, a dose to reach the PK-PD target ranged from 12-52 mg/kg (CV 102%), with a mean dose of 25 mg/kg, once daily for bacteria with a MIC value $\leq 0.25 \ \mu g/mL$.

The availability of inexpensive human generic ciprofloxacin combined with the variable oral systemic availability increases the risk that some animals are receiving inadequate antimicrobial exposure that may increase the emergence of bacterial resistance. The variable oral absorption in these dogs illustrates the difficulty in determining an effective dose for oral ciprofloxacin tablets. Obviously, some dogs may be below the therapeutic target; and some dogs above the target when an average dose is used in clinical situations. In addition, some bacteria may have higher MIC values because the CLSI breakpoint for susceptible bacteria is $\leq 1 \ \mu g/mL$, which would require an even higher dose (CLSI, 2008). A larger clinical study is underway in which a larger population of dogs of mixed canine breeds, sizes, ages, and gender will be examined.

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NOTES



CANINE MAST CELL TUMORS

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INCIDENCE, SIGNALMENT AND ETIOLOGY: The MCT is the most common skin tumor of the dog, and the second most common malignant tumor noted in the canine population. MCTs are primarily found in older dogs (8-9 yrs) but have been reported in younger dogs(1-4). Several breeds appear to be at increased risk for the development of MCT including dogs of bulldog descent (boxer, Boston terrier, English bulldog), Labrador and golden retrievers, cocker spaniels, schnauzers and Sharpeis(1, 4-6). The etiopathogenesis of MCTs in the dog is unknown, as is the reason for the extremely high incidence in this species although studies are ongoing to identify possible genetic risk factors. Interestingly, while dogs of bulldog ancestry are at higher risk for MCT development, it is generally accepted that MCTs in these dogs are more likely to be benign(4, 7).

HISTORY AND CLINICAL SIGNS: Most MCTs in the dog occur in the dermis and subcutaneous tissue. Primary MCTs may also present in other sites such as the oral cavity, nasopharynx, larynx, and gastrointestinal tract.. Visceral MCT involving the spleen, liver and/or bone is usually the result of systemic spread of an aggressive primary cutaneous MCT, although it can occur as an independent syndrome.. Cutaneous MCTs usually occur as solitary nodules, although 10 to 15% of dogs will present with multiple tumors. Approximately 50% of cutaneous MCTs occur on the trunk and perineal region, 40% on the limbs, and 10% on the head and neck. The clinical appearance of MCTs can vary widely. MCTs arising in the subcutaneous tissue are often mistaken for lipomas. In general, MCT that are slow growing and present for at least 6 months are more likely to behave in a benign manner, while those that are rapidly growing large tumors are more likely to behave in a malignant manner(8). Clinical signs are due to the release of histamine, heparin and other vasoactive amines. Mechanical manipulation of MCTs can induce degranulation leading to erythema and wheal formation (termed Darrier's sign) and occasionally, an owner will report that the tumor appears to change in size over short periods of time. Gastrointestinal ulceration is also a potential complication of MCTs and plasma histamine concentrations can be elevated in dogs with MCT, primarily those with gross evidence of disease.

DIAGNOSIS: Cytologic evaluation of fine needle aspirates is the easiest method to diagnose a MCT. Poorly differentiated malignant mast cells may contain few, if any, granules in which case special stains (toluidine blue, geimsa) may be necessary. Excisional biopsy is required for histologic grading of the tumor. If cytologic diagnosis proves difficult, a needle or punch biopsy of the tumor can be obtained prior to surgery; as release of mast cell mediators may inhibit healing resulting in excessive bleeding, care should be taken when performing a biopsy.

STAGING:

Minimum data base: CBC, chemistry panel and urinalysis should be included in the work-up of any animal suspected to have cancer. Dogs with MCTs (especially those with systemic disease) may have anemia secondary to GI bleeding.

Buffy coat smear: Dogs with many different kinds of disease, including skin and gastrointestinal diseases may have a positive buffy coat smear so this is no longer considered a useful test.

Bone marrow aspiration: While bone marrow evaluation is more likely to detect systemic involvement than the buffy coat smear, it is usually easier to find evidence of MCT in other organs (liver, spleen). Therefore, routine bone marrow aspiration is not recommended.

Lymph node aspiration: All regional lymph nodes should be carefully examined for signs of enlargement and any suspicious nodes should be aspirated for cytologic examination. Also, as metastatic nodes may palpate within normal size, it is recommended that all accessible regional lymph nodes be examined by aspiration cytology. Malignant mast cells in metastatic lymph nodes are often found in

clusters/aggregates rather than singly, aiding in a diagnosis of metastasis. If possible, lymph node aspiration should be performed prior to surgery, as post-op inflammation can result in mast cell migration to local nodes and thus confuse the interpretation.

Evaluation of thorax and abdomen: Thoracic radiographs may be included as part of staging, although pulmonary involvement is uncommon. Abnormalities reported include lymphadenopathy (sternal, hilar), pleural effusion, and anterior mediastinal masses. Evaluation of the abdominal cavity is important as spread to the liver and spleen and abdominal lymph nodes may be noted. It is recommended that fine needle aspiration of the liver and spleen be performed if abnormalities are detected during ultrasound examination, or if the dog possesses negative prognostic indicators.

PROGNOSTIC FACTORS:

Histologic grade: The histologic grade of a MCT is determined after excisional biopsy of the tumor. It is the most consistent and reliable prognostic factor and correlates significantly with survival, but it will not predict the behavior of every MCT. Furthermore, there is disagreement in tumor grading among pathologists; in one study there was significant variation in grading the MCTs, although this was found to be less so if all pathologists strictly employed the system described by Patnaik. Grade 1: these MCTs are considered to behave in benign manner and complete surgical excision is usually curative. Grade 2: These represent at least 45-65% of all MCTs reported and their biologic behavior is more difficult to predict (6, 8-10). Many dogs with complete excision of a Grade 2 MCT are cured and radiation therapy following incomplete excision of solitary Grade 2 MCTs can cure greater than 80% of affected patients(11, 12). However Grade 2 MCTs have the ability to spread to local lymph nodes, as well as distant sites, and a proportion of dogs that receive definitive therapy may develop metastatic disease. Grade 3: These tumors behave in a biologically aggressive manner, exhibiting metastasis early on in the course of disease. The mean survival time of dogs with Grade 3 MCT has been reported as 18 weeks when treated with surgery alone(8). In one study, the percentage of dogs with Grade 3 MCTs surviving at 1500 days was reported as 6%, and in another study, the percentage of dogs surviving at 24 months was 7 %(6, 13). However, with the recent use of multimodal treatment approaches, survival times of Grade 3 MCT patients are improving substantially, with many dogs now surviving to at least one year following diagnosis. Given the issues with the current histologic grading system, a new grading system has been proposed that divides MCTs into high or low grade based on one of four features identified on histopathologic evaluation(14). In this setting, tumors would be classified as high grade if they possessed 1) at least 7 mitotic figures/10 HPF; 2) at least 3 multinucleated cells/10 HPF; 3) at least 3 bizarre nuclei/10 HPF; or 4) karyomegaly. In 95 dogs with MCT evaluated by both the Patnaik and alternative systems, the alternative system was somewhat better at predicting which dogs would be more likely to die of disease. Validation of this new 2-tiered system is ongoing.

Clinical stage: Recent evidence suggests that the historical staging system for MCTs is not reflective of tumor biology. For example, there is controversy regarding the effect of multiple MCT on prognosis. Several studies indicate that there is no difference in outcome between patients with a single cutaneous MCT and those with multiple MCT while other studies have suggested an inferior outcome in dogs with multiple tumors. The effect of lymph node metastasis on prognosis is also somewhat controversial. In two studies, the presence of mast cells in the regional lymph node was a negative prognostic factor for survival and disease-free interval. (15, 16) However, an additional study revealed that dogs with Grade 2 MCT and lymph node metastasis treated with radiation therapy (RT) post surgery achieved long-term survival.(17) Other studies have shown that dogs with Grade 2 MCT with lymph node metastasis may have a good prognosis if the affected lymph node is removed and adjuvant chemotherapy is administered. For Grade 3 MCT, the presence of metastatic disease resulted in a median survival time of 194 days compared to 503 days for dogs with no metastasis.(18) For these dogs, treatment of the lymph node improved survival time (240 days) compared to those dogs whose lymph nodes were not treated (42 days). As with all cases, clinical judgment is probably important. A dog with an effaced enlarged lymph node will be more likely to fail therapy when compared to a dog with a lymph node that is not clinically enlarged but has cytologic evidence of metastasis.

Anatomic location: MCTs that develop in the oral cavity, nail bed, inguinal, preputial, and perineal regions were originally reported to behave in a more malignant fashion regardless of histologic grade.⁻ However, two reports now demonstrate that at least for definitive evidence for MCTs in the inguinal, preputial, and perineal regions this is likely to be untrue and dogs with tumors in these locations do not necessarily fare poorly(*19, 20*). Approximately 50-60% of dogs with MCT located in the muzzle present with regional lymph node metastasis, although this does not necessarily indicate a worse long-term prognosis as median survival times for dogs with metastatic disease is 14 months. MCT arising in the subcutaneous tissues have a favorable prognosis with extended survival time and low rates of recurrence and metastasis. In one study of 306 dogs with subcutaneous MCT, metastasis occurred in 4% of dogs and 8% experienced local recurrence. Conjunctival MCT were also found to have a good prognosis.

Growth rate: Tumors present for long periods of time may be more likely to be benign. In one study, 83% of dogs with tumors present for longer than 28 wks prior to surgery survived for at least 30 wks, compared to only 25% of dogs with tumors present for less than 28 wks(8).

Breed: Boxers have a high incidence of MCTs, but these tend to be more well differentiated and carry a better prognosis(4, 8). The same has been shown to be true for pugs(7).

Markers of Proliferation: Several proliferative indices have been evaluated in an attempt to predict the outcome of canine MCTs. Perhaps the most useful is Ki-67, a protein found in the nucleus the levels of which appear to correlate with cell proliferation. In one study, the mean number of Ki-67 positive nuclei was significantly higher for dogs that died of MCTs than for those that survived. For dogs with Grade 2 tumors, the number of Ki-67 was significantly associated with outcome(*13*). An additional study demonstrated that Ki-67 score can be used to divide Grade 2 MCTs into two groups with markedly different expected survival times(*21*). Mitotic index (MI, number of mitoses per 10 high power fields) may also be extremely useful for predicting the biologic behavior of canine MCTs(*22*).

Kit mutations: Kit is a receptor tyrosine kinase found on mast cells (as well as hematopoietic stem cells and melanocytes, among others) and Kit signaling is required for the differentiation, survival, and function of mast cells(23-26). Somatic Kit mutations have been identified in 30-50% of aggressive canine MCTs and these resulting in uncontrolled Kit signaling, contributing to malignant mast cell diseaes(27-30). These mutations are associated with an increased risk of local recurrence, metastasis, and death of affected dogs(30, 31).

TREATMENT

Surgery: Wide surgical excision is indicated for all canine MCTs. Historically, it has been recommended that the margins need to be at least 3 cm in each direction; deep margins are as important as the lateral margins. Recent studies demonstrated that all Grade 1 MCTs were completely excised with 1 cm of normal tissue around the MCT (lateral margins) and 1 fascial plane included in the excision (deep margin)(32, 33). Additionally, 75% and 68% of grade II MCT were completely excised with a 1 cm lateral margin and one fascial plane as the deep margin. Similarly, 100% and 89% of Grade 2 MCT were completely excised with a 2 cm lateral margin and one fascial plane for the deep margin. Neither of the studies evaluated Grade 3 MCTs. It is still recommended to take a 3 cm lateral margin and one fascial plane for the deep margin when feasible. All of the excised tissue should be submitted and margins should be labeled so the pathologist is able to specifically identify any areas of incomplete excision. However, even histologically clean margins do not guarantee that a tumor will not recur. In one study, 83% of dogs with Grade 1 MCT, 44% of dogs with Grade 2 MCT, and 6% of dogs with Grade 3 MCT were alive 1500 days after surgical excision(6). In another study, 100% of dogs with Grade I, 44% of dogs with Grade 2, and 7% of dogs with Grade 3 were alive two years after surgical excision(13). Lastly, a proportion of Grade 2 tumors that are incompletely excised will not recur post surgery. In one study, the estimated proportions of Grade 2 tumors that recurred locally at 1, 2, and 5 years were 17.3%, 22.1%, and 33.3% respectively and the median overall survival was 1426 days (34).

Radiation Therapy: Substantial data suggests that radiation therapy is effective at eliminating remaining microscopic disease following incomplete excision of Grade 1 and 2 MCT (greater than 90% three year control rate). Unfortunately, dogs with Grade 3 tumors do not fare as well; while the radiation may be effective at preventing local recurrence, many dogs develop metastasis. Radiation therapy has also been

used to treat solid MCTs (macroscopic disease) when surgery was not an option. Varying degrees of success have been found; in one study, a 50% one-year control rate was obtained. A recent study demonstrated a 60% complete response rate of MCTs to radiation when combined with prednisone and toceranib, an inhibitor of Kit (see below) (*35*).

Chemotherapy: The use of adjuvant chemotherapy is indicated for Grade 3 MCTs, metastatic MCTs, non-resectable high grade tumors, or for any other MCT with negative prognostic indices.

<u>Corticosteroids</u>: The reported response rate of canine MCT to prednisone is 20-70%, with. Partial remissions are more common than complete remissions, and at least some of the observed response may be due to a decrease in tumor-associated edema. Recent data suggest that response of MCTs to glucocorticoids is dependent on the presence of glucocorticoid receptors on MCTs.

<u>Vinca Alkaloids</u>: Single agent response rates of vincristine, vinblastine and vinorelbine are 7%, 12% and 13%, respectively, suggesting that vinca alkaloids are not effective as sole agents for the treatment of MCTs(*36-38*). Vinblastine has been combined with prednisone and/or cyclophosphamide in other studies, inducing objective responses ranging from 27-64%. Lastly, adjuvant vinblastine and prednisone therapy was used to treat dogs with Grade 3 MCTs that had undergone surgical excision resulting in survival times. During a median follow-up period of 429 days, the overall median survival time was not reached(*39*). However, dogs presenting with lymph node metastasis prior to tumor removal had a shorter median survival time of 322 days.

<u>CCNU (lomustine)</u>: In one study, 8/19 dogs (42%) with measurable MCTs had an objective response to single agent lomustine for a median duration of 77 days(40). Data suggests that the addition of CCNU to vinblastine/prednisone does not improve outcome compared to vinblastine/prednisone for the treatment of non-resectable MCTs or Grade 3 MCTs. More recently the response rate of MCTs to CCNU in the absence of prednisone was approximately 10%.

<u>Kit inhibitors:</u> Orally bioavailable small molecule inhibitors of Kit include (Palladia, Kinavet, Gleevec)(41-44). In a placebo controlled randomized study, response rate in Palladia-treated dogs was 37.2% versus 7.9% in placebo-treated dogs and the overall response rate for all dogs in this study receiving Palladia was 42.8%. The commercially available Kit inhibitor imatinib mesylate (Gleevec) has been used to treat canine MCTs. Response to therapy occurred in 10/21 dogs treated with imatinib; the objective response rate was 100% in dogs whose MCTs possessed a Kit ITD. Lastly, a randomized double blind placebo controlled phase III clinical trial of Kinavet was then performed in over 200 dogs with non-metastatic Grade II or III MCTs. While the overall RR was not significantly different between placebo and Kinavet treated dogs, there was a significant difference in time to progression between the two groups, suggesting that Kinavet has biologic activity in MCTs.

SUPPORTIVE CARE

H2 antagonists: As histamine stimulates gastric acid production by parietal cells, MCT may cause GI ulceration. To prevent this, any of the standard H2 antagonists may be utilized including cimetidine, ranitidine, or famotidine. Alternatively, proton pump inhibitors such as omeprazole may be utilized and are likely to be more effective especially in gross disease.

H1 antagonists: Massive mast cell degranulation can lead to hypotensive shock and death. Therefore, all patients with gross mast cell disease should be placed on the H1 antagonist diphenhydramine.

Sucralfate: This can be a useful adjunct if gastrointestinal ulceration is suspected secondary to mast cell disease. It should be used in conjunction with either an H2 antagonist or proton pump inhibitor.

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NOTES


THE USE OF GLUCOCORTICOIDS IN VETERINARY DERMATOLOGY

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Steroids are compounds that are manufactured from and resemble cholesterol. They get this classification as they contain a common steroid ring nucleus. Steroids are primarily produced in the cortex of the adrenal gland but other organs, such as the testicles and ovaries, also contribute to their production. Some of the metabolically active substances included in this group are the sex hormones, bile acids, and cortisone.

Those corticoids that increase gluconeogenesis (i.e. cause an increase in blood sugars and liver glycogen) are called **glucocorticoids** (**GC**). More than 95% of the secreted corticosteroids are considered GC. These are products of the inner zones of the adrenal cortex, the zonas fasciculata and reticularis. The primary physiologic corticoid is **cortisol**, also termed **hydrocortisone**. In man, cortisol is estimated to be produced at a rate of 10 mg/day. The daily production rate of cortisol can rise 10-fold in response to severe stress. In dogs, daily cortisol production is 0.2 to 1 mg/kg/day. No information is available for cats.

Cortisone is the synthetic inactive form of the hormone cortisol. The active form, hydrocortisone, is formed by dehydrogenation in the liver. If an additional double bond is synthetically added to cortisone, this results in increased glucocorticoid activity and a decreased rate of degradation. The product of this first synthetic change is **prednisone**, which is also an inactive form. Activation requires hydroxylation in the liver at the C-11position by 11 β -hydroxydehydrogenase, converting prednisone to **prednisolone**, the biologically active form. There is good evidence that horses, and possibly cats, may not convert prednisone to prednisolone in the liver, making the latter a more appropriate therapeutic choice in these species.

Methylprednisolone is formed by the addition of a methyl group to prednisolone at C-6. Adding a fluorine molecule to hydrocortisone at the C-9 position results in increased glucocorticoid but also marked mineralocorticoid activity (fludrocortisone, Florinef.) Further modification of this molecule by methylation at C-16 results in dexamethasone or betamethasone. These molecules have high GC but low MC effects.

The duration of action of synthetic GC is determined by the structure of the drug molecule. This in turn determines potency and the dosage given. Generally, the larger the dose and the more potent the glucocorticoid, the longer the drug will have an effect. (Table 1). In the clinical situation, however, the route of administration and the water solubility of the carrier substance are usually more important factors effecting the duration of action. Oral GC are generally formulated as a free base, or an ester that is digested to the free base, and subsequently absorbed. Parenteral GC (i.e. injectable) are usually esters of acetate, diacetate, sodium phosphate or sodium succinate. The sodium phosphate and succinate esters are very water-soluble and rapidly attain serum levels even when given intramuscularly. In contrast, the acetate or diacetate esters are poorly water-soluble and are slowly absorbed at a continuous low level of glucocorticoid for several days to weeks. This slow absorption may greatly prolong the adrenal suppressive effects. Concern regarding adrenal suppression is the basis for the recommendation of alternate day dosing of short acting oral GC when long-term treatment is needed.

HOW DO THEY WORK?

Glucocorticoids influence a variety of body functions because they affect most cells in the body. They exert most of their actions by blinding to intracytoplasmic steroid receptors which are then transported to the nucleus where they bind to cellular DNA and alter gene expression.

In general, GC alter carbohydrate, fat, and protein metabolism; fibroblast proliferation (important for wound healing); the inflammatory response; electrolyte and water balance; synthesis of red blood cells; central nervous system function; gastric acid production; muscle strength and function; the immune

system; and a variety of other metabolic processes. They seem to have some effect on every metabolic process.

One of the most important medical uses of GC is for their anti-inflammatory effects. GC stabilize the membranes of lysosomes so that they rupture with difficulty. This helps prevent the usual tissue damage and destruction that occurs when lysosomal enzymes are released. GC also decrease the production of bradykinin, which is a potent vasodilating substance. This decreases the permeability of the capillary membrane, which then prevents protein leakage into inflamed tissues. GC minimize the inflammatory response through the action of lipomodulin, which inhibits phospholipase A₂ which normally converts membrane phospholipids into arachidonic acid (AA), a pro-inflammatory product. The decrease in AA limits available precursor molecules for lipoxygenase and cyclo-oxygenase to produce the AA-derived mediators of inflammation. Lastly GC inhibit the expression of adhesion molecules on the endothelial cells (particularly ELAM-1 and ICAM-1) and thereby interfere with the movement of leukocytosis seen with GC administration with a concurrent paucity of GC at the site of infection.

Glucocorticoids block the inflammatory response to an allergic reaction exactly the same way that they block other types of inflammation. The basic allergic reaction between an antigen and antibody is not affected and even some of the secondary effects of the allergic reaction, such as the release of histamine, still occur. However, the subsequent inflammatory response is responsible for many of the serious and the sometimes fatal effects of the allergic reaction, administration of GC can be lifesaving.

A complete understanding of immunosuppression induced by GC is not known. The effect is more pronounced on the cellular arm than the humoral arm of the immune system. GC have minimal effects on plasma immunoglobulin concentrations but can modulate immunoglobulin function. For example, opsonization of bacteria is inhibited.

At immunosuppressive doses (the exact dose has not been scientifically determined) GC can induce decreased production of intracellular signaling cytokines such as IL-1, IL-6, TNF- α , IFN- γ and granulocyte colony-stimulating factor (GM-CSF). These are the signals that T and B lymphocytes use to communicate and will result in an alteration of the immune system at multiple stages.

Glucocorticoids cause marked changes in leukocyte numbers and distribution. A mature neutrophilia is a characteristic component of a physiologic stress response and to exogenous GC treatment. This occurs from a combination of an increased release of mature neutrophils from the bone marrow, decreased margination and decreased migration of neutrophils out of the blood vessels, resulting in a prolonged circulatory half-life.

In contrast, the administration of GC leads to a decreased number of circulating lymphocytes, eosinophils, and basophils. Lymphopenia results from a redistribution of circulating lymphocytes to nonvascular lymphatic compartments such as the lymph nodes. As lymphopenia is not a marked or consistent component of the feline stress leukogram, this species is considered relatively steroid resistant.

Systemic glucocorticoids are probably the most commonly used drugs in veterinary medicine and are undoubtedly the most commonly used and abused drugs in veterinary dermatology. Their intended and appropriate use in veterinary dermatology is for their anti-pruritic, anti-inflammatory, and immunomodulatory properties. A beneficial response is seen in animals with allergic disorders, inflammatory skin diseases, and autoimmune or immune-mediated dermatoses.

SIDE EFFECTS

As with any other class of drugs, GC have clear value when used to treat a disorder for which they have proven therapeutic benefit and when administered at the appropriate dose, frequency, and duration of administration. Their recognized anti-inflammatory, anti-pruritic and immunosuppressive effects make them a valuable addition to veterinary medicine. There is no question that side effects do occur with GC therapy. However, excessive concern for these may prevent the appropriate use of this class of drugs when they are indeed indicated. Yet GC tend to be shunned by some practitioners who worry about iatrogenic suppression of the hypothalamic-pituitary-adrenal (HPA) axis, immune suppression and other side effects.

The benefits of any therapy must always be weighed against the possible and / or probable side effects. It is well-recognized that the excessive use of GC can be associated with many adverse effects. The anti-inflammatory and immunosuppressive actions of GC, though desired for their therapeutic effects, may facilitate the establishment or spread of other infectious or parasitic diseases. As a result, dogs treated with GC have a tendency to develop secondary bacterial infections of the skin, urinary tract or respiratory tract. Urinary tract infections have been documented in 18 to 39% of dogs who are treated with 0.28 to 0.8 mg/kg of GC for more than 6 months.

The most serious side effects of GC are related to prolonged use of large doses which may suppress the HPA axis. The effects of chronic elevations in glucocorticoid levels are readily seen with naturally occurring hyperadrenocorticism (Cushing's disease). Unfortunately those same problems can be created by overuse of GC by the veterinarian and / or client, even when administered on an alternate-day basis. These high levels of exogenous steroids can result in hyperglycemia, fat redistribution, decreased skin elasticity, atrophy of the skin, poor wound healing, a pendulous abdomen secondary to a redistribution of body fat, poor quality coarse hair, alopecia (e.g. hair loss from breakage and failure to regrow), comedones (e.g. follicular plugs or blackheads), a variety of bacterial infections (especially of the bladder and skin) and even calcinosis cutis (e.g. mineral deposits in the skin). Localized dermal and adnexal atrophy following subcutaneous and occasional intramuscular repositol GC have also been reported. If the glucocorticoid used also has mineralocorticoid effects then polyuria (e.g. production of an increased amount of urine) and polydipsia (e.g. drinking an excessive amount) may also be present.

Iatrogenic secondary adrenocortical insufficiency is a side effect that can be seen after withdrawal of the glucocorticoid therapy. When an animal is treated with a glucocorticoid, the adrenal gland, in natural response to the effect of the exogenous GC on the HPA, will stop producing steroid hormones for some period of time. The duration of this suppressive effect is known to be dependent on the type of steroid and duration of treatment. However, the precise degree and length of suppression in any individual dog cannot be predicted. Generally speaking the longer the therapy and the higher the dosage, the longer the time before natural production of steroid hormones by the adrenal gland resumes. This resultant lack of endogenous (physiological) GC is the cause of weakness and possible circulatory collapse that can with cessation of exogenous glucocorticoid therapy.

One intravenous injection of dexamethasone at 0.1 mg/kg, which equals approximately 3 mg of hydrocortisone (cortisol) or 3X the highest daily natural production can suppress the HPA for 32 hours in a healthy dog.

CONTRAINDICATIONS TO THE USE OF GLUCOCORTICOIDS

Because GC cause an elevation in blood glucose, caution should be exercised when they are administered to animals with diabetes mellitus. Concurrent use with non-steroidal anti-inflammatory drugs should be minimized due to the increased risk of intestinal ulceration. The use of GC should be avoided in pregnant animals as they can induce parturition. And congestive heart failure has been reported in a few cats as a possible side effect.

USE OF GLUCOCORTICOIDSS IN VETERINARY DERMATOLOGY

The major indications for the use of GC in veterinary dermatology include treatment of allergic or pruritic dermatoses, autoimmune dermatoses and feline eosinophilic granulomas.

The use of glucocorticoids is an art that requires the clinician to skillfully integrate the many details about the patient, the owner, and the disease so that an appropriate type and dose of glucocorticoid can be used. Changes and adjustment in dosages and even the type of GC used must be made depending on the response of the disease and the side effects that develop. Physiologic doses of GC are those that approximate the daily cortisol production by normal individuals. In dogs, daily cortisol production has been reported to be 0.2 to 1 mg/kg/day. A pharmacologic dose of GC exceeds physiologic requirements. There is no optimal dosage established in the veterinary literature and each case should be treated individually. There are guidelines, however, which serve as a good starting point. Using oral prednisone or prednisolone (or methylprednisolone) in dogs as the drug of choice the recommendations are:

Antipruritic doses: 0.5 mg/kg/day for 7 to 10 days then decreased to lowest

effective dose

Anti-inflammatory doses: 1.0 - 1.5 mg/kg/day for 7 to 10 days then decreased

to the lowest effective dose

Immunosuppressive doses: 2.0 – 6.0 mg/kg/day for induction then decreased

as possible to maintain control of the disease

Compared with dogs, cats seem to require about twice the dose of oral GC to achieve the same effects.

LONG TERM USAGE OF GLUCOCORTICOIDS

This section now presents my personal beliefs regarding a safe dose of GC used long term as there is no true evidence-based formula. Every animal and every disease condition differs.

The following is my formula for dogs. Starting with the fact that dogs manufacture 0.2 to 1 mg/kg/day of cortisol and need this to survive, and using a 40 kg dog as an example:

40 kg X 0.4 mg X 365 days = 5840 mg of cortisol produced / year (I chose 0.4 mg as it's on the lower side of the mid range for production)

Since prednisone is considered to be about 4 times as potent as hydrocortisone (cortisol), dividing 5840 by is 1460mg of prednisone. Thus, this 40kg dog would "see" in a normal physiologic state approximately 1460 mg of prednisone (or prednisolone) / year

From these calculations I have I have developed what I called my "safe annual steroid dose" formula:

BW (kg) X 30 = mg prednisone / year

or BW (lb) X 15 = mg prednisone / year

This number (30) is based on a combination of several publications reporting the side effects of GC as related to dose and on over 10 years of using this in my own practice and seeing the safe use.

Again considering the 40kg dog I would calculate

 $40 \times 30 = 1200$ mg of prednisone to be the "safe annual steroid dose". This value is less than the range of what is considered physiologic for that dog.

If a dog requires more than what I believed to be the "safe annual dose" of prednisone or prednisolone to control its dermatologic disease (i.e. pruritus from allergies or atopic dermatitis) then I would either add a second medication in an effort to decrease the amount of GC needed or change medications (e.g. to cyclosporine.) Steroid treatment protocols generally begin with higher doses and then are tapered but again looking at these calculations in this way can be helpful guides.

If the dog needed more than the "safe annual steroid dose" and the owner declined further diagnostic work up or other therapy then I recommend monitoring for weight gain and urinary tract infection as these are the most common side effects recognized with ongoing GC therapy. First, I would discuss in detail my recommendations for feeding and have the dog weighed to make sure that it wasn't gaining weight. I would also perform a cystocentesis for urinalysis and urine culture and sensitivity test. It is critical that the urine be cultured as in dogs receiving steroid therapy due to the dilution of the urine and the anti-inflammatory effects of the steroids, actual bactiuria or the suggestive urinalysis findings of infection may not be detected. Although it would be expected that the urine specific gravity to be low (about 1.012), if there was protein or glucose in the dilute urine a serum chemistry to assess for any early renal disease or diabetes would be indicated. I would expect the alkaline phosphatase and alanine aminotransferase (ALT) to be elevated as well as for the CBC to reveal a stress leukogram.

In summary, the rational use of glucocorticoids in veterinary dermatology requires the clinician to be familiar with the pharmacological and physiological effects and side effects of steroids as a class and the

individual formulations used in their practice .Glucocorticoid use should be limited and kept to a minimum by using adjunctive therapies (such as antibiotics, antihistamines, topical therapies, etc.) whenever possible. A diagnosis should be made prior to determining the therapeutic regimen. And long-term therapy should be monitored with frequent examinations and laboratory testing as indicated.

Table 1

Comparison of Water-Soluble Glucocorticoids Used in Dogs and Cats

Generic Drug	Relative	Relative	Equivalent	Plasma Half-	Biologic Half-
	Mineralocorticoid	Glucocorticoid	Dose	life	life in Humans
	Potency	Potency	(mg)	(Hours)	(Hours)
		(Anti-inflammatory	_		
		Potency)			
Hydrocortisone	1	1	20	1	8-12
Prednisone /	0.8	1	5	(2) 1	12.26
prednisolone	0.8	4	5	(?) 1	12-30
Methylprednisolone	0.5	5	4	1.5	12-36
Triamcinolone ^a	0	3 - 5	4	(?) 4	24-48
Flumethasone		15	1.5		
Dexamethasone	0	29	0.75	2	35-54
Betamethasone	0	30	0.6	(?) 5	>48

^a Triamcinolone acetonide has a greater potency (approaching that of dexamethasone)

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Figure 1



NOTES



SKIN BARRIER AND THERAPY

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Introduction

Much attention has been devoted in recent years to skin barrier function in dogs. The main disease that has triggered this interest is canine atopic dermatitis. Although some questions are still raised on the degree and role played by skin impairment in canine atopic dermatitis, most studies have demonstrated some level of skin abnormality in dogs with atopic dermatitis, functionally, chemically, and ultrastructurally. These studies have sparked interest in the concept of skin barrier repair and its role in improving clinical signs of allergies. Limited published information exists on skin barrier impairment in other skin conditions thus the focus of this lecture will be on the role of skin barrier repair in allergies and more specifically in canine atopic dermatitis.

How do we assess skin barrier function and the efficacy of treatments?

Great effort has been put in both human and veterinary medicine to identify suitable treatments to improve skin barrier. The idea is that improvement of skin barrier should result into improvement of clinical signs. That seems to be the case in humans with atopic dermatitis where a good correlation exists between severity of clinical signs and degree of skin barrier impairment. In dogs, this correlation is not always evident, at least based on pilot studies considering transepidermal water loss (TEWL). This lack of detectable correlation may be due to technical issues rather than due to lack of relevance. Although the measurement of TEWL is commonly considered as a non invasive method to assess skin barrier function, in veterinary medicine this methodology has been shown to provide variable results. The lack of reliability in TEWL measurements therefore creates challenges when treatment options aimed at repairing skin function are evaluated for efficacy. Thus, the evaluation of usefulness of new treatments should be done in multiple ways and not only rely only on TEWL measurements.

Both topical and with systemic treatments can have an effect on skin barrier. It is important to note also that the vehicle used for any topical treatment can also have an effect on skin barrier and, with chronic use this impact can be significant, as demonstrated in human medicine.

Skin barrier impairment can be the results of both primary and secondary issues. While in human medicine there is ample evidence of primary defects in proteins and enzymes involved in skin barrier function, the evidence of a primary defect in dogs is still lagging. Skin barrier repair in veterinary medicine can be done either by addressing the inflammation, which has a negative effect on skin barrier function, or by addressing some of the chemical deficiencies reported in the stratum corneum of dogs with atopic dermatitis.

Therapy with ceramides, essential fatty acids, and moisturizing products

In both humans and dogs with atopic dermatitis, impairment of skin barrier function has been linked, at least in part, to ceramides deficiency. Thus, topical application of ceramides has been explored to normalize lipid abnormalities. In dogs it has been shown that normalization of lipid composition is detectable after just 3 weeks of topical therapy with sphingo-lipids. In recent studies, ceramides, free fatty acids and cholesterol were all found to be lower in the skin of untreated dogs with atopic dermatitis than in normal dogs, and the topical treatment with sphingo-lipid emulsion resulted in significantly increased values for cutaneous ceramides. The normalization of lipids showed also a relationship with normalization in ultrastructure. The ultrastructural and chemical benefits with the topical application of sphingo-lipids are echoed in clinical trials. An open study in dogs with atopic dermatitis showed clinical improvement with twice weekly application of a combination of ceramides and fatty acids for 12 weeks with significant improvement of clinical scores and erythema noticeable as early as after 6 weeks. The

dogs selected in this clinical trial had chronic disease and had failed other treatments making these results even more encouraging. Excoriations and alopecia were also improved after 6 weeks of therapy while more chronic changes (e.g. lichenification) did not show significant change in the course of the study. No evaluation of pruritus was done in this study. Another double-blinded, placebo-controlled study applying the same emulsion three times weekly for 4 weeks reported significant decrease of clinical signs when compared to the control group. The results on TEWL in such study were mixed. Thus, topical application of ceramides can be beneficial in allergic patients and requires multiple applications per week. It is important to stress that the benefits are not immediate and that may be best used in combination with other treatments to make the patient comfortable while waiting to achieve the full benefit.

Essential fatty acid therapy has been considered both topically and systemically for skin barrier repair. An open study that used a spot-on (once weekly) and a spray (once daily) containing essential oils and unsaturated fatty acids for 8 weeks showed decreased of clinical scores and pruritus significantly in both groups with no difference between groups. No improvement on TEWL was found. Oral administration of essential fatty acids for 2 months also improved the ultrastructure and increased the lipid content in the skin of atopic dogs. This feature was observed both with free and protein-bound lipids. No evaluation of correlation with clinical improvement was reported. The improvement after oral administration of essential fatty acids is consistent with other studies that showed how diet plays an important role in skin barrier. In one study it was found that a combination of pantothenate, choline, nicotinamide, histidine and inositol, when fed at supplemented concentrations, was able to significantly reduce TEWL in dogs after 9 weeks.

There are many other products on the market labeled for skin barrier repair. The ingredients range from ceramides precursors (e.g. phytosphingosine) to combinations of humectants. Although the theory behind the use of these products is reasonable, there is very little evidence to guide the clinician in terms of what is really effective. Very few studies have been done and most of the information is still anecdotal.

One interesting study evaluated the effect of ultrapure soft water (UPSW), water in which calcium and magnesium ions have been replaced with sodium ions, on skin barrier and found beneficial effects compared to tap water. In a randomized, controlled, cross-over study, shampoo treatment with UPSW significantly decreased pruritus and dermatitis scores, whereas shampoo treatment with tap water did not.

Correction of the inflammation

As mentioned above, skin barrier impairment in dogs may be due to a combination of primary and secondary factors. A recently published study suggests that ceramides deficiency is actually at least in part secondary to inflammation. For these reasons it is reasonable to believe that skin barrier function would improve when inflammation decreases. Indeed a recently published study in dogs with atopic dermatitis showed that topical treatment with a glucocorticoid (0.0584% hydrocortisone aceponate spray) significantly improved skin barrier and clinical signs after 14 days of therapy. This study was an open study and the spray was used once daily to the lesions of all dogs for 7 or 14 days. Clinical assessment was performed before (day 0) and after treatment (day 14), and clinical responses were correlated with changes in skin barrier function. A positive response was found for both clinical severity of lesions and pruritus. A significant reduction of TEWL was also documented at the end of the study. No skin biopsies were taken in this study to investigate the effects of this topical on lipids and ultrastructure of the stratum corneum. It is important to note that chronic use of strong topical glucocorticoids may actually worsen skin barrier due to cutaneous atrophy and disruption of lipid metabolism in the stratum corneum. This has been demonstrated in humans but has not been addressed in dogs yet.

Another approach to decrease inflammation in dogs with atopic dermatitis is the use of oral cyclosporine. A yet unpublished pilot study comparing the effects of oral cyclosporine with the ones of oral prednisone

on skin barrier function as measured by TEWL in dogs with naturally occurring atopic dermatitis showed no significant effects of time nor group after 4 weeks of therapy. This finding may be due to the variability of TEWL measurements. A recently published study supported a possible beneficial effect of cyclosporine on the innate immune barrier of skin. Additional studies are needed to better investigate the long term effects of anti-inflammatory therapy on skin barrier function in allergic dogs.

In summary, the field of skin barrier repair is still in infancy in veterinary medicine and much work needs to be done to investigate the long term effects of many products that have been labeled for skin barrier repair. It is reasonable to speculate that early intervention using skin barrier repair treatments could benefit allergic dogs and minimize the risk for allergic sensitization. It is however important to remember that not every product containing humectants and emollients is suitable for long term use and that it is crucial to investigate in depth the effects of these therapies before recommending them long term. At this point in time, the topical product for which there seems to be more evidence and support is an emulsion of sphingo-lipids. For this formulation there is a published medium term study (12 weeks) and there has been documentation of a positive effect on chemical and ultrastructural components of the skin barrier. There is also support to indicate that these changes are reflected in an improvement of clinical signs.

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NOTES



HOW TO INTERPRET BIOPSY RESULTS

Dr. Pamela E. Ginn

WHEN-

Severity, chronicity, type of treatment being considered, differential?

WHERE- Selecting the Site(s) Key is often more than one site- usually cost the same

Primary- the change that is most representative of the disease, just developing to fully developed

Secondary- evolution of the lesion over time Crusts and more crusts- almost always useful** Different types of lesions- the range Alopecia- mild to severe, choose skin normally well haired Pigment changes- try to get marginal region

WHAT-



Punch- not good for large vesicles or pustules, good for very small or very widespread changeconsider the twisting motion and size of instrument

Wedge/incisional/ellipse- good for marginal biopsies, deep lesions such as panniculus, areas that might be easier to close than with a punch- footpad, nose

Shave- often very useful, small, delicate animals, shallow (surface, epidermis and very superficial dermis, no suture, thin saucer shape

Excisional-large, suspect possible neoplasm

(All Images from Pathologic Basis of Veterinary Disease 5th edition Eds. Zachary and McGavin Elsevier 2012 Chapter 17 The Integument Ann Hargis and Pamela E. Ginn) HOW-

Preparation- clinical appearance determines how much can be done without jeopardizing the integrity of the sample- basically do not disturb surface if there are surface lesions, just clip long hair

Temperature - avoid freezing or heat damage- cautery, lasers...

Avoid injections of local anesthetic into the dermis

Handling- small gauge needle, avoid forceps

Fixative- formalin almost always all you need, must be essentially IMMEDIATE

Labeling- separate containers if distinctly different lesions thought to represent separate processes - such as neoplasms, otherwise one container is fine

> ink, dyes, containers, sutures, cassettes, adherence to cardboard (not useful most of the time- falls off or gets dried out too much)

Sending- what is your time line, how secure is your carrier?

WHAT TO INCLUDE

Complete history: age, breed, sex, color, complete description of character and distribution of the lesions, presence of pruritus, duration of lesions, symmetry, treatment successes, failures, ancillary testing, pictures

WHO- Choose a Veterinary Pathology with interest/expertise in dermatopathology

Recommendations -veterinary dermatologists, AAVD, other colleagues Learn about their practice Communication - with the pathologist reading your submissions Fit your style- phone, email, text, reports Timeline- reasonable, can you expedite if needed? Cost structure-

Numbers of samples, special stains, special requests Additional sections, levels

Report itself

Format- what suits you

How you receive your reports- fax, email, web account Basic parts of full report-

Accession data

Gross Evaluation, dissection, tissue handling

Description

Morphologic Diagnosis

Comment-Subjective interpretation-an opinion!

DEFINITION AND APPEARANCE OF CLINICAL LESIONS WITH HISTOLOGICAL **CORRELATIONS**



Epidermal collarette



Excoriation





























Primary Lesions

Macule Papule/ nodule Plaque Tumor Pustule/Vesicle/Bulla Wheal

Secondary Lesions

Scale Crust Scar Erosion/Ulcer Excoriation Hyperpigmentation Hyperkeratosis Lichenification Fissure

EPIDERMAL CHANGES

Acanthosis = hyperplasia - thickening due to increased numbers of nucleated cells in the epidermis. The stratum spinosum usually increases in width leading to rete ridge formation. Hyperplasia can be regular (typical of psoriasiformdermatosis) with even size of the rete ridges or irregular with uneven size of the rete ridges (most common). The hyperplastic epidermis can also form papillated (surface projections) protrusions typical of warts or papillomas.

Hyperkeratosis - refers to increases in the thickness of the stratum corneum. Hyperkeratosis can occur non-specifically secondary to trauma or inflammation or as a specific characteristic of certain diseases.

Orthokeratotic hyperkeratosis- build up of excess keratin after normal cornification has occurred (cells have lost their nuclei). The buildup can be due to excess production or lack of exfoliation of keratin.

Parakeratotic hyperkeratosis refers to thickening of the stratum corneum with retention of nuclei. The retained nuclei indicate the process of cornification is abnormal. Parakeratotic hyperkeratosis can be an indication of several different diseases entities such as the superficial necrolytic dermatitis or zinc responsive dermatosis

Dyskeratosis - Refers to the premature keratinization of cells within the epidermis. Dyskeratotic cells are rounded up, hypereosinophilic and have nuclear degeneration. Dyskeratosis is common with parakeratosis and usually is accompanied by a degree of hyperplasia. It is often a feature of epidermal dysplasia seen as a pre-neoplastic change prior to the development of a squamous cell carcinoma.

Apoptosis: Individual programmed cell death. Usually seen in the basal layer but can become transepidermal in some disease states. Apoptotic keratinocytes resemble dyskeratotic keratinocytes and are shrunken and hypereosinophilic. Apoptosis may be a feature of some immune mediated diseases such as systemic lupus erythematosus or in conditions such as erythema multiforme. Ultraviolet radiation can also lead to apoptosis of keratinocytes referred to as "sunburn" cells.

Necrosis: Many causes such as physical injury (laceration, burns) chemical exposure as in irritant contact dermatitis, ischemia (vasculitis, thromboembolism), adverse drug reactions such as toxic epidermal necrolysis.

Atrophy: Thinning of the epidermis due to decrease in the number and size of cells of the epidermis. Atrophy is a consequence of sublethal injury. The most common cause is endocrine

dermatoses but may also occur with partial ischemia or malnutrition. Distribution of the atrophy and other changes will help indicate cause.

Abnormal fluid accumulation in between cells of the epidermis or within the individual cells of the epidermis.

Intercellular epidermal edema = Spongiosis. Spongiosis is due to fluid exudation into the epidermis and results in widening of the spaces between keratinocytes. Spongiosis occurs commonly with inflammation but is a characteristic feature of certain specific entities: contact irritant dermatitis, feline eosinophilic plaque, seborrhea, thallium toxicosis, and zinc responsive dermatosis. Severe spongiosis can lead to vesicle formation.

Intrakeratinocyte fluid accumulation = keratinocyte degeneration due to fluid accumulation in the cells. The cells look enlarged and are pale staining. There are two types: hydropic and ballooning degeneration. The change can be laminar meaning it affects all the cells within a certain layer of the epidermis. Typical of the superficial necrolytic dermatitis.

Hydropic degeneration is a type of intracellular fluid accumulation that affects the basal layer or outer follicular root sheath and can result in separation of the epidermis and dermis. Clefts can lead to vesicles. Vesicles can lead to ulcers. Hydropic degeneration is usually seen in dermatosesthat are damaging some component at the dermal epidermal interface-such as SLE, drug eruptions and dermatomyositis.

Ballooning degeneration - markedly swollen, eosinophilic keratinocytes usually in the more superficial layers of the epidermis. This change is most frequently associated with a viral infection. Ballooning degeneration can lead to vesicle formation.

Acantholysis - loss of cohesion between keratinocytes. Breakdown of intercellular attachments can occur via immune destruction as in pemphigus (Type II cytotoxic hypersensitivity) or by neutrophilic enzymatic destruction. Acantholytic cells are usually associated with the formation of pustules, vesicles, bullae or clefts at some level of the epidermis. The exact location of this separation is very important in specific disease diagnosis (subcorneal, intracorneal, suprabasilar, subepidermal). The fluid that accumulates between the cells forms the vesicle or pustule.



Vesicles and bullae - Refer to fluid filled spaces within the epidermis or at the epidermal/dermal junction. Vesicle < 1.0 cm; bullae > 1.0 cm. Either can form secondary to marked spongiosis, ballooning degeneration, hydropic degeneration, acantholysis or basement membrane damage (freezing, heat, friction), immune destruction of dermal epidermal adhesions (bullous

pemphigoid) or in diseases with genetic defects in structural molecules (epidermolysisbullosa). Viral diseases often lead to vesicle or bullae formation due to their cytopathic effects on keratinocytes. The level of vesicle formation within the epidermis is often indicative of the disease process present.



A. Subcorneal B. Suprabasal

C. Subepidermal

Pustules - Collections of fluid and inflammatory cells in the epidermis or subepidermal region. Neutrophilic Pustules: Common in bacterial infections and in some autoimmune skin diseases.

Eosinophilic Pustules: Most common in parasitic diseases but also seen in allergic, immune, microbial, and some idiopathic diseases.

Pautrier'smicroabscesses: A microscopic abscess specific for epitheliotropic cutaneous lymphoma (Mycosis Fungoides). Actually a collection of neoplastic lymphocytes with the epidermis.

Crusts - surface collections of plasma, leukocytes. May also contain erythrocytes and acantholytic keratinocytes. Most vesicles, bullae, and pustules (primary lesions) are fragile and transient so you are more often presented with crusts (secondary lesions)

Changes in Pigmentation: Changes in pigmentation include hyperpigmentation, hypopigmentation, and pigmentary incontinence.

Hyperpigmentation: increases in melanin in the epidermis and possibly in dermal melanophages. Nonspecific change that occurs in any chronic dermatitis.

Hypopigmentation= Most often acquired due to damage to melanocytes and adjacent keratinocytes or basal layer, leading to pigmentary incontinence. Can be seen in lupus erythematosus, drug eruptions, pemphigus, mycosis fungoides, vitiligo. Very characteristic of the uveodermatologic syndrome (aka; Vogt-Koyanagi-Harada;VKH syndrome). Pigmentary incontinence refers to the loss of melanin from the basal region of the epidermis due to basal cell damage. The melanin is phagocytosed by macrophages in the superficial dermis.

FOLLICLES

Follicular Hyperkeratosis: similar terminology to epidermal hyperkeratosis. Predominant follicular hyperkeratosis occurs in primary seborrhea, vitamin A responsive dermatosis, endocrine dermatoses and others.

Comedones-cystically dilated follicles

Follicular atrophy: physiologic; or pathologic-shrinking of hair follicles typically seen in endocrinopathies, ischemia.

Follicular dysplasia - refers to abnormal development of hair follicle that leads to alopecia usually associated with uncommon coat colors (blue, fawn) in the condition known as Color Mutant Alopecia. Others are associated with black hair and abnormal melanin production and accumulation. Microscopically, the hair follicles are deformed.

Folliculitis: hair follicles are the primary focus of the inflammatory infiltrate.

Luminal folliculitis suggests bacterial (Staphyloccocal), fungal (dermatophytosis), or parasitic disease (demodicosis).

Mural folliculitis refers to conditions in which leukocytes target the wall of the follicle for instance in the feline mosquito bite hypersensitivity (eosinophilic mural folliculitis). Bulbar folliculitis- Alopecia areata, a condition leading to well demarcated zones

of alopecia, is characterized by a lymphocytic bulbar folliculitis.



DERMAL CHANGES

Angioedema and urticaria = hives. Urticaria is edema of the dermis while angioedema also involves the subcutis. Both usually seen with Type I hypersensitivity reactions (insect bites or stings, vaccine reactions, food allergy, atopy, drug reactions).Nonimmunologic causes include heat, cold, sunlight.

Fibrosis: Increase in collagen and fibroblasts, the end result of tissue repair that may be preceded by formation of granulation tissue, essentially a scar. May occur secondary to chronic trauma, inflammation.

Collagen degeneration or collagenolysis: Collagen can become granular and fragmented and have altered staining qualities such as increased eosinophilia or basophilia.

"Flame Figures" - granular eosinophilic debris on and around collagen seen with diseases with eosinophilic infiltrates and may be a product of degranulatedeosinophils. Seen in mast cell tumors, arthropod bites, eosinophiliccollagenolytic diseases.

Collagen mineralization: most often a form of dystrophic mineralization seen in hyperadrenocorticism. Can be metastatic as in Vit D/Ca/Phos imbalance. Some cases are idiopathic.

Collagen atrophy: decrease in size of collagen bundles most commonly seen in the cat with hyperadrenocorticism or other severe catabolic states. The entire dermis is thinner than normal, translucent, very fragile and easily torn.

Elastin changes - Solar Elastosis: Increases in production of elastin by fibroblasts that are not functioning normally as a result of chronic actinic damage. Often seen along with sun induced squamous cell carcinomas.Most common in the horse. The dermis contains large number of thick, wavy basophilic elastin fibers.

SUBCUTIS

Panniculitis: The panniculus may be the primary site of inflammation or secondarily involved with spread of dermal lesions. Infectious agents are common causes of panniculitis. Fat Necrosis: may occur anytime there is inflammation. Necrotic fat is often seen in cases of atypical mycobacteriosis of cats. Damaged adipocytes release lipid into areas of inflammation. Can also see fat necrosis in lupus and rabies vaccine reactions, trauma to the panniculus, or in cases of pancreatitis.

VESSELS

Vasodilation: Congested vessels may lead to grossly visible erythema seen with many types of skin injury.

Vasculopathy/Vasculitis: Vascular injury leads to edema, hemorrhage, ischemia, necrosis. May see ulceration or sloughing of extremities. Usually a feature of Type III hypersensitivity reactions (immune complex disease) but may have a number of causes. Consider SLE, septicemia, DIC, toxins, frostbite, cold agglutinin disease.

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NOTES



BUGS, DRUGS AND THE PATH TO LEAST RESISTANCE: ANTIMICROBIAL STEWARDSHIP IN THE 21ST CENTURY

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INTRODUCTION:

With the acquisition of drug resistance rapidly outpacing the development of new antimicrobial drugs, the crisis of antimicrobial resistance has exploded onto the scene in the 21st century. Antimicrobial resistance has been listed as a top threat to global health and a top priority of multiple national and international human medical and public health agencies¹, including the World Health Organization (WHO), International Society for Infectious Diseases (ISID), Center for Disease Control and Prevention (CDC), American Society for Microbiology (ASM), Infectious Disease Society of America (IDSA) and the American Medical Association (AMA). The American Veterinary Medical Association (AVMA) has also created steering committees and task forces, published a position statement and supported the development of species-specific position statements by associations including the American Animal Hospital Association (AAHA) and American Association of Feline Practitioners (AAFP). However, in spite of recognized need, we still lack a system for monitoring antimicrobial resistance and use, and therefore lack a sound metric against which to measure successes or failures as we attempt to change our practices across the profession in response to this crisis.

EMERGENCE OF MULTI-DRUG RESISTANT BACTERIA:

Antimicrobial resistance is not a new phenomenon. Long before we discovered our first antibiotic and harnessed it for the treatment of disease, the production of antibiotics and the subsequent development of resistance in exposed microbes was a way of life for bacteria, fungi, plants and animal as they engaged in the trans-generational struggle for survival and competition for resources. To this day, many of our mainstay drugs are derived either directly or indirectly from nature, and the majority of these from bacteria. By these same mechanisms, exposure of bacteria to antimicrobial drugs administered for therapeutic purposes drives the development of resistance to those drugs. However, instead of localized exposure within a micro-environment, drug therapy involving parenteral administration of high drug concentrations results in unprecedented exposures of both pathogens and innocent bystanders. Rapid evolution and spread of resistance in bacteria is facilitated by a short generation time as well as by mechanisms of sharing genetic material that are unique to prokaryotic cells. Transfer of resistance genes can be made not only to progeny cells via vertical gene transfer but also to related or unrelated cells via conjugation (transfer of plasmids via sex pili from one consenting adult bacterium to another) and transformation (uptake of functional genetic material from the environment in the form of naked DNA and subsequent integration and expression of the acquired genes)².

With increasing selective pressure in increasingly concentrated settings of antimicrobial use and immunecompromised patients, human hospitals have been a primary setting for the development of multidrug resistant bacteria. However, in veterinary medicine the outpatient/community setting has been of equal or greater importance, and antimicrobial use in agriculture has also contributed to the spread of antimicrobial resistance. In the face of this growing and unprecedented selective pressure, the pace of new antimicrobial drug development has slowed, and to compound matters, the focus of drug development has been biased towards broad rather than narrow spectrum drugs. This has created what is referred to as "the perfect storm" of antimicrobial resistance³.

Although as health care professionals veterinarians are far from alone in the inappropriate use of antimicrobials, various practices in the veterinary profession have already come under scrutiny and ongoing scrutiny of our drug use can be expected. In small animal clinical practice in particular, we are currently provided great freedom in our access to antimicrobial drugs under the Animal Medicinal Drug

Use Clarification Act of 1994 (AMDUCA), with the implicit trust that veterinarians will make judicious decisions in the use of these drugs. The components and conditions of AMDUCA have recently come onto the radar of antimicrobial use task forces, and increasing restrictions on the use of antimicrobials in veterinary medicine may be forthcoming not only in agricultural and production animal medicine but also in small animal clinical practice, particularly if the profession does not proactively address our role in this crisis⁴.

ANTIMICROBIAL STEWARDSHIP:

Stewardship as a general term is defined as the careful and responsible management of something that does not belong to you but has been entrusted to your care. Specifically, antimicrobial stewardship in medical practice refers to a rational and systematic approach to the use of antimicrobial agents that optimizes outcome on both the individual and the population level⁵. This includes appropriate case selection, optimal drug selection, and optimal dosage and duration of treatment, with "optimal" defined to include the the best clinical outcome for the treatment or prevention of infection as well as the least possible impact on subsequent development of drug resistance. An important point to keep in mind is that it is not possible to have zero impact on the development of antimicrobial resistance unless you are not using antimicrobial drugs^{2,5}.

Studies in human medicine have shown that up to 50% of antimicrobial use is inappropriate⁴⁻⁶. This includes use of antibacterial medications for the treatment of syndromes not caused by bacteria, treatment for culture results that reflect colonization or contamination rather than infection, administration of broad spectrum antibiotics where narrow spectrum agents would be equally effective, prescription of antibacterial therapy courses that are longer than necessary, and prescription of antibacterial agents at inappropriate doses. No similar studies have been performed in veterinary medicine, but the expectation is that such studies would confirm similarly widespread misuse.

Clinical Best Practices: In attempting to improve your antimicrobial stewardship, whether in your individual practice or in a formal approach to hospital policy, it is helpful to use the 4 Ds of antimicrobial stewardship as guidelines⁷:

- 1. Right drug: The right drug is based either on culture and susceptibility testing or solid clinical support for the presence of infection coupled with predictable bug-drug combinations for the clinically diagnosed infectious disease. Whether treating based on culture results or empirically, the most narrow spectrum drug to which the infectious agent is expected to be susceptible and which will reach adequate concentrations at the site of infection is the drug of choice, except in cases where contraindicated based on patient risk.
- 2. Right dose: Missed doses are probably the most significant cause of incorrect dosing in veterinary medicine, taking us into the arena of client compliance. Dosing schedules that take into consideration the client's schedule are essential, but has led in veterinary medicine to significant over-use of broad spectrum drugs that have longer dosing intervals. Under-dosing is more common in large breed dogs and has increased potential to promote resistance, whereas over-dosing is more common in small breed dogs and is capable of driving the development of drug resistance but also puts the patient at increased risk for the development of adverse drug reactions..
- 3. Right duration: Inappropriate duration can mean stopping too soon or treating for too long. Determining the right duration can be challenging, but an important rule of thumb is that any therapy of greater than 10 days duration should be based on culture results. If empiric therapy initiated for a suspected infection is unsuccessful after 10 days, discontinuing therapy and

obtaining a sample for culture is indicated. Continuing therapy long term, adding additional drugs or switching to a broader spectrum of drug is not practicing good antimicrobial stewardship.

4. De-escalate to pathogen directed therapy: the 4th D applies to therapy initiated in the interim between submitting samples for culture and obtaining final culture results. Whenever possible, the culture results should be used to narrow the spectrum of activity of the prescribed drug. This often means changing therapy after 3-4 days when culture results are available. When culture results are negative, unless there is strong reason to suspect that a negative culture result is a false negative, antimicrobial therapy should be discontinued. Finishing out the course of therapy when an infection is subsequently ruled out is not recommended.

To Treat or Not to Treat: What is not addressed by the 4 D's is possibly the most common category of misuse in veterinary medicine, and that is prescription of antibacterial drugs when a bacterial infection is not present. If there is not clinical support for infection, the appropriate antimicrobial drug, duration and dose are irrelevant – no antimicrobial drug is the right drug. Therefore, it is essential to focus on clinical decision making, diagnostic algorithms and appropriate use and interpretation of in-house and laboratory tests as a component of our antimicrobial stewardship practice. Having infection as a differential diagnosis is not alone sufficient justification for antimicrobial therapy. To test the strength of the differential, ask yourself what infectious agent(s) would be most likely, based on signalment, clinical signs, and the nature of the lesion(s) and system(s) involved. If there is a high index of suspicion for neoplasia, autoimmune disease or other non-infectious disease, the use of antimicrobial therapy to "rule out infection" in lieu of or prior to performing indicated diagnostic testing is not good antimicrobial stewardship or good medicine. The use of antimicrobials, even when indicated, is always associated with risk and will always do some degree of harm, and it is therefore critical that we appropriately balance risk with potential benefit, and harm with potential good.

Infection vs. colonization: Another important point to remember is that positive culture growth does not necessarily prove cause and effect. Therefore, even when a positive culture is obtained, thoughtful and critical evaluation of the results in conjunction with the entire clinical picture is required in order to decide whether to treat, or, in a mixed infection, which organisms to treat for. Ideally, your microbiology laboratory will support you in this decision making process and in the practice of good antimicrobial stewardship by reporting susceptibilities only for organisms likely to represent infection rather than colonization (normal microbiota or transient colonization) or contamination, and by suppressing results for broad-spectrum, late generation or other "big gun" drugs for isolates where a narrow spectrum drug is an appropriate choice. Cultures yielding heavy mixed growth are particularly problematic, and interpretation of results from skin and ears is arguably the most challenging at both the laboratory and the clinical level. Utilizing a laboratory with practices founded on knowledge of veterinary microbiology and dermatology will help maximize the value of culture results. The indiscriminate testing and reporting of all isolates is not good diagnostic microbiology and is not in accordance with CLSI guidelines. On the other hand, clinical correlation is essential and will sometimes argue in favor of working up and treating for an isolate which is not normally considered pathogenic (i.e., in an immune-compromised patient), so appropriate communication with the laboratory is also required.

Dolor, calor, rubor, tumor and functio laesa: Remember the cardinal signs of acute inflammation. Although not definitive for infection, when present they are supportive. On the other hand, the absence of these cardinal signs should cause you to place infection lower on your list of differentials. Chronic inflammation may lack heat and redness, it may or may not be painful, but it will exhibit some form of "tumor" (firm swelling, thickened or lichenified skin) and will manifest some degree of loss of function. Chronic infections are also typically more difficult to treat than acute infections as well as less predictable in regards to etiology, and therefore confirmatory laboratory testing is indicated. Appropriate diagnostic workup will also allow discrimination from non-infectious disease that would benefit from timely

intervention. When infectious, chronic conditions require longer treatment duration may require culture both prior to and during treatment to assess response/adjust therapy if indicated.

Culture based vs. empiric therapy: Ideally an infection is confirmed with culture. Maximizing the diagnostic value of this test requires thoughtful selection of cases for culture, appropriate sample collection, handling and submission, and selection of a quality microbiology laboratory. Initiating therapy in the absence of culture results can be done when there is sufficient clinical evidence for infection, life threatening illness that is either likely to be infectious or carries significant risk for complication by secondary infection, or potential for significant and possibly irreversible injury to the patient if an infection is present and left untreated while awaiting culture results. In some cases, highly characteristic clinical signs, quick bench tests and established empiric guidelines for therapy may allow treatment without necessity for culture. Antibiograms and in-house Gram stains can greatly facilitate rational clinical decision making and should be utilized as indicated to guide treatment decisions.

The Gram stain: The Gram stain is fast and relatively easy to perform as an in-house test to complement cytological evaluation when infection is suspected. Gram stain kits are inexpensive and the stains have long shelf lives when stored properly. A Gram stain can be used to help determine whether infection is likely to be present by identification of organisms that may be more difficult to identify in Diff Quik preparations and/or by further characterizing the organisms identified in regards to their cell wall. Remember, finding microorganisms does not necessarily confirm infection, particularly when we are talking about skin cytology. However, if treatment is supported, the morphology and Gram staining properties of the organism(s) will help choose the most appropriate first line therapy. If you identify bacterial rods on cytology which do not stain with Gram stain, particularly if this is in a context of granulomatous inflammation, a mycobacterial infection becomes your top differential diagnosis. Altered staining of microorganisms due to loss of viability or prior antimicrobial therapy (particularly with cell wall-active agents) can confound interpretation of the Gram stain and diminish its clinical utility. When first introducing this stain in your practice it is advisable to use Gram positive and Gram negative controls with each slide in order to refine your technique.

Antibiograms and your clinical microbiology laboratory: As our profession examines our role in stewardship, we need to work cooperatively with our diagnostic laboratories. In human laboratory medicine, accredited microbiology laboratories are required to provide their clients with antibiograms in accordance with CLSI guidelines⁸. The antibiograms are used by physicians and hospital infection control teams to guide empiric therapy, monitor trends in resistance, establish antimicrobial use guidelines that support good antimicrobial stewardship, and then measure the success (or lack thereof) of those guidelines in reducing the incidence of antimicrobial resistance. Because it is not required in our profession, very few veterinary microbiology laboratories compile and share antibiograms with their clients, and the majority of veterinarians are not asking for them because they don't know what they are. A few veterinarians are proactive enough to compile data and produce their own hospital antibiograms as part of a formal infection prevention and control program. However, while these can be extremely useful in monitoring for breaks in infection prevention and control procedures, they do not allow monitoring more broadly of local and regional trends. And, unlike human hospitals, even the largest veterinary specialty centers won't have sufficiently robust data on which to base empiric treatment decisions. Making the data of veterinary testing laboratories available would not only support good stewardship at the practice level, but would also address a key issue identified in virtually any evaluation of the veterinary profession in regards to stewardship and management of the global antimicrobial resistance crisis: that is, the lack of broad-scale surveillance data on antimicrobial resistance. An integrated data base compiling results from all laboratories performing veterinary microbiology testing is the holy grail of antimicrobial resistance surveillance for our profession. If this information were already captured for the production of annual antibiograms, this could be readily accomplished.

CONCLUSION:

In order to do our part in managing the growing crisis of antimicrobial resistance, it is essential that veterinary practitioners engage in the practice of good antimicrobial stewardship. Showing that we are good stewards is essential if we hope to retain the current levels of access to drugs and freedom to prescribe drugs needed for treatment of our patients, patients. The practice of antimicrobial stewardship is also part of good medical practice, and by adhering to these guidelines we can therefore also exercise improved, evidence-based clinical decision making and provide improved patient care. Guidelines developed and published by professional organizations are a starting point but they do no good if they are not followed. As these policy statements indicate, increased education, surveillance and research are also needed. As a profession, we have an opportunity to show sustained and strong leadership in our response to this crisis. Like all such opportunities, taking advantage requires action and change.

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NOTES



TRUE OR FALSE? WHAT TO DO WHEN YOUR CULTURE RESULTS DON'T FIT THE CLINICAL PICTURE

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INTRODUCTION:

Culture-guided therapy is an essential component of good medicine and good antimicrobial stewardship. In many cases, culture results confirm clinical suspicion of infection and allow selection of an appropriate antimicrobial drug, leading to a clinical cure of the infection. In other cases, negative culture results support clinical suspicion that bacterial infection is not present and provide additional support for additional work up for and treatment of non-infectious disease. But there are also times when the culture results, in ways large or small, do not correlate with the clinical picture. In such cases, it can be difficult to determine whether to disregard results, repeat cultures, or re-consider your clinical differential diagnosis. There is no cut and dry answer and the majority of such determinations will have to be made on a case by case basis. The exception to this is when questionable results represent a trend, in which case examination of all stages of the process on a more broad scale level are indicated. In either situation, an understanding of the testing process and a close working relationship with your microbiology laboratory will greatly enhance your ability to deal with these challenges when they arise.

A TOUR OF THE MICROBIOLOGY LABORATORY:

My experience in talking to veterinarians is that not very many of us have a clear understanding of what is actually involved in working up a culture and producing a microbiology report. The following summary will serve as a very basic survey of the function and work flow of the microbiology laboratory.

After receiving and accessioning, samples received for cultures will be "set up" – that is, they will be inoculated onto agar plates and possibly also broth medium, with the number and exact types of media used in the setup dictated by the source and tests requested as well as on the specific protocols of a given laboratory. It tissue is submitted, it is macerated to create the inoculate. Fluid other than urine is centrifuged to produce a concentrated pellet for inoculation. Urine cultures are set up using a calibrated loop so that results can be quantified as colony forming units per ml of urine. Plates are then incubated overnight and evaluated daily for culture growth.

Gram stains (and other special stains, if indicated) are performed after all plates are inoculated. Gram stains are read out to provide preliminary information to the clinician and are also used as a benchmark of comparison when evaluating growth, if positive. If multiple cultures are ordered for a single swab or if only a small amount of material is collected on a swab submitted for culture, the material remaining by the time the Gram stain is performed will be scant. This is the most common reason for Gram stain results that do not correlate with culture growth.

Once growth is noted, it is semi-quantified (except for urine) based on laboratory standards as scant (or rare), light, moderate or heavy. When multiple isolates are present the plates may require sub-culturing (re-streaking a single colony onto a new plate and re-incubating) to be certain of isolation prior to performing any further testing. If highly fastidious organisms are suspected as the cause of infection the medium and oxygen concentration for incubation may be adjusted to inhibit more rapid growing organisms that could obscure or prevent growth of potential pathogens. Cultures with heavily mixed growth from a normally non-sterile such as the skin may be more supportive of contamination or colonization than of infection, and these cases are particularly problematic for the laboratory microbiologist. In these cases, specific information as to site including nature and distribution of lesions is used to make determinations of which, if any of the isolates should be selected for susceptibility testing.

A single, isolated colony of an isolate selected for susceptibility testing will be used to create a standardized dilution for inoculation based on optical density, then tested for susceptibility to an appropriate panel of drugs based on the organism and site of potential infection. Most laboratories perform automated serial dilutions to determine minimum inhibitory concentrations. These automated panels may be supplemented with additional drugs tested by Kirby Bauer disk diffusion method or (less often) by E-test. The automated results are typically interfaced so that they run directly from the testing equipment into the laboratory information system where the culture report is produced. Rules of interpretation are programmed to over-ride MIC results and report as resistant if indicated based on supplemental resistance testing that is either included on the automated panels or run separately at the bench and entered into the results database for the case. Results of KB tests are manually evaluated, zone sizes are measured, and results entered manually either by the microbiologist or by support staff. Result updates are sent daily and the cases are finalized once the culture is complete, typically in 3-5 days.

What should be clear to you after this "tour" is that, while automated where possible, the nature of diagnostic microbiology is significantly more subjective, less amenable to automation, and involves significantly more human decision making than other areas of clinical laboratory testing. The experience and knowledge of the microbiologists working the bench are therefore a critical component of the quality and accuracy of these test results.

THE THREE PHASES OF LABORATORY TESTING:

Laboratory testing is sub-classified into three phases for the purposes of process evaluation, quality control and improvement and the identification, correction and prevention of laboratory errors. The first is the pre-analytical stage, which includes specimen collection, transport and processing. Phase II is the analytical phase, during which the actual testing of the sample is performed. This can be a technically simple and automated process, such performing a serum chemistry panel, or technically intensive and only partially automated process, such as reading culture plates and performing susceptibility testing as indicated based on culture results. Phase III includes results transmission, interpretation, follow up and retesting.

Errors in specimen collection and submission: These are pre-analytical errors that occur in the clinic or hospital. Potential errors include incorrect site preparation, inadequate material collected, loss of viability after collection due to exposure to formalin or oxygen (for strict anaerobes), desiccation, or improper/expired transport medium. Another potential error is ordering the wrong tests – if higher bacteria such as mycobacteria or nocardia are suspected, these will not be isolated in routine cultures due to specific growth requirements and slow growth of these organisms.. Mislabeling of samples or failing to label samples is a common error in veterinary medicine. Although unlabeled samples will not be rejected for testing in veterinary diagnostic laboratories, an absence of a specimen label decreases certainty of identification and increases the risk of mixing samples in the laboratory. Because of the unacceptable risk of error associated with mis-labeled or unlabeled samples, in human diagnostic laboratories, samples received without 2 unique patient identifiers matching on the sample and test request form will be rejected.

Errors in specimen processing: These are pre-analytical errors that occur during the accessioning, test ordering and set up of cultures, and can include mixing up of patient samples, ordering the wrong test, failure to inoculate the correct plates or contamination of the plates or the submitted sample during inoculation.

Errors in analysis: For cultures, errors made by technicians can include incorrect identification of organisms, failure to identify a significant organism in a mixed culture, selection of the wrong isolates for susceptibility testing, incorrect concentration of the inoculums used for the susceptibility testing, failure to perform indicated testing for resistance mechanisms or and failure to flag discrepant results for

verification. Errors occurring during the automated phase include equipment failures, quality control breaks such as use of expired disposable products or mutated QC organisms.

Errors in reporting: Incorrect programming of suppression and reporting rules can cause isolates to be reported as sensitive in spite of overriding results of supplemental resistance testing. Manual data entry errors can also occur. Failures in communications technology can result in reports not being received in a timely fashion

Errors in interpretation: One potential error of interpretation is to trust your results too much – remember, not all false negatives are erroneous: In addition to errors, there is the potential for false negative results to occur that are not attributable to any error on the part of the humans involved in this process but rather to the vagaries of biology itself. Some bugs lose viability in spite of you doing everything right. Some pathogens will fail to grow under laboratory conditions altogether, and should be considered along with other potential causes of a false negative if the clinical presentation supports infection but cultures are negative.

On the other end of the spectrum, when you write off a negative result off as incorrect or convince yourself that infection is caused by non-pathogenic bacteria isolated in culture, you may be making the error of trusting the process too little. Be willing to question your initial assessmet – don't be closed to the possibility that what you think is infectious is in fact not. Biopsies are indicated in challenging cases and can help to determine whether a negative culture result is likely to be correct. Biopsy may reveal that infection is in fact present but that it is not bacterial, or it may reveal a non-infectious cause for the clinical signs/lesions.

In some cases, suspected error may be based on the failure of a "culture-confirmed infection" to respond to drugs reported as susceptible. There are a number of reasons this may occur. The organism you are treating for may not be the cause of the disease, which may be caused by an organism that was overlooked or that did not grow, or it may be non-infectious and the bacteria represent colonization. Finally, it is important to remember that in vitro susceptibility testing does not have a 100% correlation with in vivo efficacy of that drug.

Communicate: Evaluating potentially erroneous culture results is significantly more difficult to do if you are not able to question, request validation, discuss potential discrepancies, trouble shoot results and seek input for planning how to move forward. Having a good relationship with your microbiology laboratory can therefore be critical to this evaluation.

CONCLUSION:

Multi-institutional studies performed over the years in human laboratory medicine show that increased scrutiny and quality control at the laboratory level coupled with increased automation have resulted in a marked decrease in errors occurring in the laboratory with minimal change in the errors occurring in the early pre-analytical and late post-analytical phases³. As a result, the majority of errors are now occurring either before the samples are received by the laboratory or after the results have been reported to the requesting clinician⁴, and accrediting organizations are now pressuring the diagnostic laboratories to take more responsibility for the control of these types of errors as well. It warrants repeating that this is not a reflection of increased errors occurring in the clinic or hospital setting, but rather, a marked decrease in errors occurring in the laboratory. I share this more as a point of interest than as a point of comparison. Certainly it is not reasonable to extrapolate from this that a similar trend will have occurred in veterinary medicine, as we do not have the same regulatory vigilance in laboratory QC/QA, nor do our laboratories bear the weight of these costs. It is therefore imperative that veterinary practitioners advocate for their patients by taking personal responsibility for minimizing harm and unnecessary cost due to erroneous laboratory results. Part of this can be accomplished by enacting steps of process analysis, quality control on your end to minimize the occurrence of pre-analytical errors that are within your control. It is also

essential to be an educated and critical user of your laboratory services in order to minimize or fail to recognize errors that occur during the phases of laboratory testing that are not under your control. While cost and convenience are certainly important, veterinarians should also be certain to weigh reliability, quality control, availability of consultations and responsiveness to questions regarding potential laboratory errors as factors in our decision making processes when we select a diagnostic laboratory.

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NOTES



EQUINE ALLERGIC DERMATITIS

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The primary clinical signs of equine allergic skin disease have been documented to be pruritus and/or urticaria (1, 2). The pruritus and urticaria may make a horse unrideable and irritable. Additionally, pruritus can lead to severe excoriation and secondary infections. Reported causative agents include foods, weeds, trees, grasses, molds, insects and storage mites (1,2,3). The role of insect bite hypersensitivity in allergic dermatitis is being studied (6,7).

Equine allergic dermatitis resembles atopic dermatitis. Currently, research has confirmed the role of IgE in equine allergic disease and a genetic background is suspected with a potential risk allele identified (4,5). Although, it may be debatable, I will refer to equine allergic dermatitis as equine atopic dermatitis. Despite an amazing amount of research in atopic dermatitis in various species, management is still a challenge. "Finding an effective and *safe* systemic agent for the chronic management of moderate to severe atopic dermatitis remains the dermatologist's "holy grail." (9)". The diagnosis and management of allergic dermatitis is challenging in horses.

MY APPROACH TO EQUINE ALLERGIES

I currently consult on equine cases in Southern Idaho and Northern California. My approach to equine allergic dermatitis may differ from dermatologists practicing in other geographic locations. In Northern California, I practice in the greater Sacramento Valley which has a large amount of agriculture, high pollen levels and a high incidence of allergic disease. Boise, Idaho is also an agricultural valley. Other than temperature and flora differences, the valleys are quite similar.

DIAGNOSTIC STEPS

I try and approach horses as I would a dog or a cat with skin disease.

The history is very important in determining if the horse has allergies. I ask owners the age of onset, progression of disease, what medications have helped, are other horses affected, stabling conditions, current diet and worming schedule.

I perform cytology to rule out infections. Although uncommon, I have identified bacterial and Malassezia overgrowths/infections. The majority of my equine patients do not have secondary infections, but I think it is important to perform the basic dermatology diagnostic tests (cytology and skin scrapings).

If the history and clinical signs are compatible with allergic dermatitis, I will then start a work up for allergies.

CUTANEOUS ADVERSE REACTIONS TO FOODS

Adverse reactions to foods have been reported to cause urticaria, pruritus or both. Additionally, the pruritus has been reported to occur in the perianal region or tail (1). In my practice, cutaneous adverse reactions to foods are rare. In the few horses that I have been able to identify an adverse reaction to foods, the primary culprit has been oats. Scott reported alfalfa, barley, bran, oats, wheat, concentrate and feed supplements as the cause of cutaneous adverse food reactions (1). The diagnosis of cutaneous adverse food reactions in horses is difficult because elimination diets are a challenge. If I suspect an adverse reaction to foods, I will have the owner feed alfalfa exclusively for 4 weeks. If there is no relief, I will change to grass hay for 4 weeks. If the symptoms resolve, I will start an individual ingredient trial. The owners will feed the horse the possible offending foods one at a time. It should be noted that hays may be contaminated with weeds, grasses and pollens making a true elimination diet very difficult. Also, owners may not be willing to discontinue treats and supplements. Additionally, horses are often allowed to graze which may complicate the diet trial.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is the most common disease I manage in my equine practice. I include insect hypersensitivity with environmental allergies as I manage them the same. Most of my equine patients seem to have some level of insect hypersensitivity. In 2006 I reported on a survey of horses with atopic dermatitis and have expanded that survey for this presentation. This is not to be considered a statistically significant study, but is to be used to elucidate the clinical signs seen in horses in Northern California and Southern Idaho and the effectiveness of therapy. A similar study was reported by Stepnik in 2011 (10).

SURVEY

In 2006, I had 22 clients respond to the survey. I repeated the survey in 2012 and had 45 respondents out of 71 surveyed. Currently, I have 22 horses that are actively receiving immunotherapy.

We often use seasonality to help differentiate between food reactions and environmental allergies. Additionally, seasonality is important in formulating allergen specific immunotherapy (IT). The majority (80%) of horses in my area reported seasonal symptoms. Interestingly, in my previous survey, only 59% were reported to be seasonal. Clearly, as the numbers of respondents increase, the data will be more reliable. I believe the change is a reflection of increased numbers of respondents, rather than a change in allergic disease.

In dogs, it has been reported that the age of onset of atopic dermatitis is 6 month to 3 years. In horses, my clinical impression is that the age of onset is more variable. In the current survey, the reported age of onset was 6.5 years of age with a range of 7 months to 18 years. In my previous survey, the average age of onset was 5 years of age with a range of 2 to 12 years. In the Stepnik study, the age of onset was 1 to 22 years of age with a mean of 9.6 years. The results are very similar between all 3 surveys and I find it very difficult to use the age of onset of clinical signs as a reliable indicator of atopic dermatitis in horses.

Previously a variety of breeds have been reported as predisposed to allergic skin disease (1, 2, 10). In the Stepnik study only the Hackney Horse was significantly at risk (10). In the current survey of 71 horses, 57 had the breeds reported. 21/57 were quarter horses, 4/57 Arabs, 5/57 Morgans, 8/57 Warmbloods and 7/57 Thoroughbreds. This may be a reflection of the overall population of horses rather than any significant breed predilection.

Of the 71 horse owners that were surveyed, 45 owners responded. The owners were asked to respond to the success of the IT with 0-10% = poor, 10-25% = fair, 26-50% = good and 51-100% = excellent. Good to excellent responses were reported in 32/45 (71%). Of those 32, 24 were excellent and 8 good. Interestingly, 17 of the reported excellent responders have stopped IT due to resolution of clinical signs. In the previous survey 82% of owners reported a good to excellent response. I cannot explain the decrease in successrate, however there were a lot of owners that did not respond to the survey and many of those are still receiving IT.

In Stepnik's study, the owner reported success was 84% (10). Tallarico reported a success rate of 92% (11). These studies demonstrate the effectiveness of IT in horses with allergic dermatitis.

In my clinical experience, horses respond very well to IT, owners are generally statisfied and I rarely need to add additional medications. In most horses, I generally perform intradermal allergy testing, but in horses that are unable to stop medications, I will perform in vitro allergy testing.

Management of the immunotherapy is very important to success. I have found that some horses require a lower concentration of allergens. I continue at weekly intervals until there has been a good response and then increase the interval between injections. Constant dose and frequency adjustments are necessary for

a good response. I will adjust based on the horse's response. For example, if the horse is itchier after an injection then we need to decrease the strength. On the other hand if the horse is itchier before an injection interval may need to be shortened.

HEADSHAKING

Currently there are 6 horses that have received IT for headshaking. One owner did not respond to our survey. Of the 5 respondents 2 reported excellent success, 2 good and 1 fair. This is an area that needs to be explored further.

We still have a long way to go to understanding allergic disease and improving our management of these cases.

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BREED	DOB	DATE ACQUIRED	AGE ACQUIRED	AGE OF ONSET	SEASONAL	Seasons	тсну	HIVES	SWELLING	HEAD SHAKING	RESPONSE	STILL RECEIVING IT
unknown	1987	3/1/2004	18	8	ou	no	٢	٢	N	N	excellent	N
Quarter	Mar-95	3/1/1995	0	4	yes	spring-summer	у	У	N	N	excellent	N
Morgan	May-99	9/1/2003	4	6	yes	summer	y	N	Z	N	fair	N
Morgan	Jul-99	8/1/2001	4	4	ou	no	۲	N	N	N	poor	N
Oldenberg	Jun-96	6/1/1996	0	8	no	no	у	у	N	Ň	excellent	N
Oldenberg	Jun-89	10/1/2000	11	13	yes	spring/fall	y	У	N	N	excellent	y
Quarter	Mar-98	5/1/2001	3	4	yes	summer	N	Y	N	N	excellent	N
Appaloosa	Jun-99	6/1/1999	0	2	yes	spring-summer	Y	z	N	N	excellent	Y
Quarter/Arab	May-89	4/1/1994	5	5	no	no	٢	٢	z	N	excellent	N
Quarter	May-00	11/1/2003	3	3	yes	spring/fall	Y	۲	Y	N	excellent	N
Shire/TB	Jul-97	7/1/2002	5	9	yes	Spring/fall	z	z	z	7	excellent	z
Paint	May-98	12/1/2003	5	9	yes	Spring/fall	۲	z	N	N	good	N
Trakhener	May-87	6/1/1993	9	6	no	no	Y	Y	Y	N	excellent	N
TB	May-87	3/1/1994	7	12	yes	spring-summer	N	N	N	Y	good	N
Quarter	May-95	5/1/1998	3	5	yes	spring-summer	۲	Y	N	N	excellent	N
Quarter	Jan-95	12/1/2000	5	6	no	no	Y	N	N	N	fair	N
Fresian X	Jan-92	1/1/2001	6	11	no	no	Y	N	Y	N	excellent	N
Trakhener	May-90	2/1/1996	9	9	yes	summer	у	Y	N	N	excellent	Y
Arab	May-95	4/1/2000	5	6	yes	spring	Y	Y	N	N	excellent	N
Morgan					yes		Y	٢	Z	N	excellent	N
Quarter	Jan-95	1/1/1998	3	5	yes	spring-summer	Y	Y	N	N	excellent	N
TB	May-96	11/1/2002	6	7	yes	summer	N	Y	N	N	excellent	N
Morgan	Oct-90	10/1/1990	0	18	yes	summer	Y	Y	N	N	excellent	Y
Mustang	Dec-04	12/1/2004	0	3	yes	spring/summer/fall	٢	N	Y	N	poor	N
TB/Warmblood	Aug-88	1/1/1990	2	4	yes	spring	Ľ	у	u	u	poor	N
Lipizzan	Apr-99	4/1/1999	0	8	yes	spring	N	Y	Y	N	good	N
Lipizzan	Jan-98	1/1/1998	0	5	yes	spring	N	N	Z	۲	good	N
Morgan	Jan-95	1/1/1996	1	7	yes	fall	N	Y	N	N	excellent	N
Oldenberg	Apr-00	8/1/2001	1	6	yes	summer	Y	N	N	N	good	N
Warmblood	Feb-95	10/1/2004	6	10	yes	spring-summer	Y	z	N	N	good	Y
Hanovarian	1995	1/1/1997	2	5	yes	summer	٢	z	Y	N	excellent	Y
Mustang	Apr-81	1/1/1989	8	11	yes	spring-summer	≻	z	z	z	excellent	N
	Sep-02	1/1/2004	2	4	٢	summer	۲	z	z	z	poor	N
Quarter							≻	۲	z	z	excellent	٢
Quarter	1/1/1997	1/1/1998	-	4	٢	spring-summer	≻	≻	z	7	fair	N
TB	Jul-97	7/1/1997	0	9	y	summer	۲	٢	N	Z	Good	Y
Quarter	Jul-02	1/1/2003	0.5	6	Y	summer	Y	Y	Y	N	fair	Y
	Mar-01	1/1/2005	3	3	y	spring-summer	z	۲	۲	N	good	Y
Percheron	Sep-01						N	N	N	٢		۲
Quarter	Jun-04	1/1/2007	3	5	no		٢	z	N	N	fair	N
Quarter	Jan-04				٢	spring-summer	7	z	z	z		N
					٢	spring-summer	۲	z	z	Z		z
Quarter	5/1/2004	5/1/2004	0	7 m	٢	Fall	z	z	z	۲	excellent	z
Quarter	Apr-04						z	≻	z	z		z
	Sep-96	10/1/2011	5	10	по						excellent	٢
NOTES

HOW I APPROACH CRUSTING SKIN DISEASES IN HORSES

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Most equine dermatoses – whether inflammatory or neoplastic – can become crusted a some point.^{1,2} I am going to continue my comments to dermatoses that are primarily crusted at presentation, and that have no significant associated visible or palpable mass (nodules, plaques, tumors, cysts, abscesses) (Table 1). It is useful to prioritize crusting dermatoses on the basis of the region(s) of the body affected (Table 2).^{1,2}

The approach to these dermatoses begins with a thorough history and physical examination. Laboratory tests are selected (or not) based on a prioritized (which is geographically variable) differential diagnosis.^{1,2}

Investigations may include skin scrapings, trichography, cytology, clture, biopsy, therapeutic trials, and combinations of these.

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Dermatosis	Prevalence in My Practice	
Actinic keratosis	Rare	
Adverse cutaneous drug reaction	Uncommon	
Bacterial folliculitis	Common	
Besnoitiosis	Extremely rare	
Cannon keratosis	Rare	
Chorioptic mange	Common	
Dermatophilosis	Common	
Dermatophytosis	Common	
Insect bites	Common	
Linear keratosis	Rare	
Molluscum contagiosum	Extremely rare	
Onchocerciasis*	Extremely rare	
Pelodera dermatitis	Extremely rare	
Pemphigus foliaceus	Uncommon	
Sarcoid (flat)	Common	
Sarcoidosis	Rare	
Unilateral papular dermatosis	Rare	
Zinc-responsive dermatosis	Extremely rare	

 Table 1. Dermatoses Primarily Characterized By Crusts

*Is it making a "comeback"?

Body Region	Differential
Face, head, ears, neck	Actinic keratosis, bacterial folliculitis, besnoitiosis, dermatophilosis, dermatophytosis, insect bites, linear keratosis, Molluscum contagiosum, onchocerciasis, pemphigus foliaceus, sarcoid (flat), sarcoidosis
Dorsum	Bacterial folliculitis, dermatophilosis, dermatophytosis, linear keratosis, sarcoidosis, unilateral papular dermatosis
Ventrum	Insect bites, Molluscum contagiosum, onchocerciasis, <i>Pelodera</i> dermatitis, pemphigus foliaceus, sarcoid (flat)
Legs	Bacterial folliculitis, besnoitiosis, cannon keratosis, dermatophilosis, dermatophytosis, chorioptic mange, insect bites, pemphigus foliaceus, sarcoid (flat), sarcoidosis

Table 2. Body Distributions of Crusting Dermatoses*

*Adverse cutaneous drug reactions can mimic anything.

NOTES



EQUINE PASTERN DERMATITIS (EPD)

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INTRODUCTION

Equine Pastern Dermatitis (EPD) is not a single disease, but a cutaneous reaction pattern of the horse. EPD should be considered a syndrome, rather than a diagnosis.^{1,2} Uncovering the underlying etiology prior to treatment is key to minimizing treatment failures and frustration. To achieve a positive therapeutic outcome, treating the predisposing and perpetuating factors are just as important as addressing the primary cause of EPD.² This seminar reviews clinical signs, differential diagnoses, diagnosis and treatment of EPD.

CLINICAL SIGNS AND PATHOGENESIS

EPD can affect any breed of horses, but is most commonly seen in Draft horses.^{1,2} Feathering over the pasterns is a predisposing factor.^{1,3} EPD occurs without a sex predilection and is seen mostly in adult horses.¹⁻⁴ The dermatitis usually affects the caudal aspect of the pasterns, with the hind limbs most commonly affected.^{2,5} If not addressed, the lesions can spread anteriorly to involve the front of the pastern and fetlock areas.^{1,2} The lesions are bilaterally symmetric however, they can affect just one limb. Lesions are more often detected on, but not limited to the non-pigmented areas of the pasterns.⁵ Clinical signs will vary depending on the etiology, duration and previous therapy. Initially, there is edema, erythema and scaling which rapidly progresses to exudation, matting of the hair, and crusting.^{1, 2, 5} If the underlying cause is vasculitis, ulcers may be noted.^{2,5} Secondary bacterial infection is a common complication and perpetuating factor.^{1,2} With chronicity the skin may become thickened and fissured due to the constant movement and flexion in this area.⁵ The lesions are often painful and can result in lameness.⁵

There are 3 different presentations;

(1) Mild Form-(Scratches, Mud Fever, Mud Rash). This is the mildest and most prevalent form of EPD. There is alopecia, dry scales, and crusts. The skin can be thickened, and pruritus and pain is variable.

(2) Exudative Form-(Grease Heel, Dew Poisoning). This type is a more exudative form of EPD. You may observe erythema, erosion, alopecia, and serous to purulent crusting dermatitis. Often accompanying epidermolysis and vasculitis are present.

(3) Chronic Proliferative Form-(Grapes, Verrucous pododermatitis).^{2,7, 7a} This form is characterized by excessive granulation tissue (fibroblastic proliferation) that becomes cornified. Nodular proliferations of hyperkeratosis and lichenification can be seen. Fissures and papillomatous areas may develop and their formation is a common sequela in Draft breeds.^{2,6,7}

A condition characterized by progressive swelling, hyperkeratosis and fibrosis of the distal limbs in Shires, Clydesdales and Belgian Draft horses has been under investigation at the University of California, Davis.⁸ The clinical signs and pathological changes are similar to a condition in humans known as chronic lymphedema or elephantiasis. Factors that have been proposed to contribute to this disease are abnormal functioning lymphatic system in the skin, which causes severe swelling and fibrosis, a compromised immune system and secondary skin infections.⁹ The lesions do not respond well to therapy. As the disease progresses and becomes more chronic, the enlarged lower extremity becomes permanent and the swelling is firm on palpation.⁹ There is progressive skin fold and nodule formation that are first noted on the posterior aspect of the pastern. With chronicity the nodules and folds occupy the entire lower extremity. Overtime the affected limb will result in mobility problems and are often traumatized during normal exercise. The prognosis is poor due to the development of secondary infections, poor response to therapy, systemic illness, and debilitation. Recently however, the group at UC Davis studied combined decongestive therapy (CDT), which includes manual lymph drainage (MLD) and subsequent bandaging with short stretch bandages.^{9a} With the CDT, a mean volume reduction of 4.75–21.74% was achieved

resulting in increase mobility and purposeful movement. As CDT is not readily available in Canada, the author has used an oral medication combining low dose dexamethasone along with trichlormethiazide, a diuretic. This combination of medications has been licensed for treatment of udder edema in cattle and is sold as Naquasone® in an injectable or bolus form. Formulated into an oral paste, it offers cost effective palliative therapy for the CPL equine owner.

Pastern Leukocytoclastic Vasculitis (PLV) (photo-aggravated vasculitis) is an additional clinical cause of EPD. This disease is poorly understood and affects mature horses. It is unique to the horse and affects primarily unpigmented distal extremities.^{5,10} It is believed to be an immune-complex disease.⁵ If immune complexes are involved in the pathogenesis, their deposition in the distal limbs may be due to regional vasculature differences.⁵ Clinical signs suggest it is a photo-aggravated condition and hence is seen mainly in the summer. Lesions are multiple and consist of well-demarcated circular painful, erythematous, exudative, tightly adherent crusts. Patients often present to orthopedic surgeons with a suspicion of a muscle tear or skeletal injury.^{10a} The medial and lateral aspects of the pasterns are the areas most commonly affected. Lesions appear painful rather than pruritic. Edema of limb and lameness is a common sequela. Chronic cases may develop a rough or warty surface.⁵ Differential diagnoses for dermatitis of the distal limbs that is not restricted to non-pigmented skin include, but are not limited to primary irritant or allergic contact dermatitis, pastern folliculitis/pyoderma (e.g. Staphylococcus infection, Dermatophilosis), chorioptic mange, dermatophytosis, Malassezia infection, immune-mediated dermatitis (e.g. pemphigus foliaceous) and neoplastic conditions (e.g. sarcoids). Obtaining a complete history, thorough physical examination, skin scrapings, skin cytology and biopsy of primary skin lesions early in the course of disease development may increase the likelihood of reaching a definitive diagnosis.

DIAGNOSIS

A detailed history is very important in the dermatologic work up of EPD.^{5,6} Important pieces of information include; age of onset, month of the year that problem was noted, whether the EPD has been seasonal/non-seasonal or pruritic/non-pruritic. Additional questioning should include use of any overzealous use of topical medications or home remedies prior to your examination. Details should include what topical and systemic medications have been used and if lesions improved or worsened with each treatment. Environmental conditions can be a predisposing or primary factor in EPD, and when possible a detailed description or personal inspection of environment (bedding, pasture, sand, insect burden, moisture) should be done. Primary irritant and allergic contact dermatitis may involve the pastern region.^{1,5,6,11} Chronic exposure to moisture such are wet bedding or muddy pastures appears to be the most common cause for irritant contact dermatitis. Draft horses have long hair in the fetlock and pastern region which increases the retention of moisture and contributes to the maceration of the skin.^{1,5,6,7}

Usually, in cases of contact irritant or allergic dermatitis all four pasterns are affected. Be sure to ask whether or not other animals or humans in contact with the affected horse, are affected as well (infectious or zoonotic, i.e. dermatophytes). Recurrences may also be related to the conformation of the food and pastern.^{7a}

Pastern folliculitis/pyoderma is caused by two main types of bacterial infections in the horse: Staphylococcus aureus and Dermatophilus congolensis.^{1,6,7,11} Initially, papules and/or pustules (rare) will be noted with a staph infection, however with chronicity they may not be seen. A biopsy for culture would be needed for a definitive diagnosis. The area would need to be surgically scrubbed and biopsy taken with sterile precautions. Taking a swab of the area and culturing can be misleading due to surface contamination. Dermatophilus congolensis may also cause pastern dermatitis.^{1,6,7,11,11a} The lesions typically are crusting and exudative and when crusts are removed the skin is ulcerative.^{12,13} A requirement for this organism to cause infection is chronic moisture and trauma.^{11a,12,13} A genetic susceptibility may exist. Immuno-compromised and malnourished horses are far more susceptible but serious infections can occur in almost any horse.^{11a} Immunity is short-lived so recurrent infections may occur. Please see below for collection, staining and microscopic examination for this organism.

Dermatophytosis (Trichophyton equinum) rarely causes pastern folliculitis, however it is important to rule out.^{1,6,7,11} A definitive diagnosis requires a positive DTM culture in conjunction with positive microscopic identification of macrocondia.

Chorioptic mange may be the underlying cause of pastern dermatitis and must be excluded.^{1,6,7,11,13,14} Draft horses are predisposed due to the long hairs over their pasterns.⁵ This condition is intensely pruritic. Affected horses may constantly rub the area, and often are observed stamping his feet.⁵ This should be highly suspected if others in contact are affected and have clinical signs of pruritus. Mites are easily identified if infested.

Both systemic and contact forms of photosensitization may involve the pastern regions of the horse with white extremities.¹⁵ When contact is involved usually just the muzzle and extremities are involved. Primary photosensitization is due to a preformed or metabolically derived photosensitizing agent reaching the skin by ingestion, contact or injection. Hepatogenous photosensitization is due to blood phylloerythin levels that are elevated in association with liver abnormalities and a photodynamic agent.^{5,15,16} Each type will cause dermatitis in the presence of UV light. The most common cause of equine contact photosensitization is exposure to clover pastures.⁵ Other causes of primary photosensitization are Saint John's Wort (Hypericum perforatum), Buck wheat (Polygonum fagopyrum), and Perennial rye grass (Lolium perenne).^{15,16}

DIAGNOSTIC TESTS

Superficial Skin Scrape

Rule out superficial mites, especially Chorioptes spp. This can be done using a #10 blade (dull). Superficially scrape crusts and debris onto slide or others recommend using a stiff scrubbing brush or denture type tooth brush to sweep the dander, crusts and debris into a container.^{4, 14} Examine immediately under the microscope 10X objective, placing debris in mineral oil and using a cover slip. Some authors suggest applying a small amount of insecticide to the slide because these mites are very fast.¹⁷

Acetate Tape Preps-Diff Quik

Evaluate for secondary bacterial and Malassezia spp. infection. These two organisms are often perpetuating factors. Observing under a microscope at 100X for cocci shaped bacteria +/-degenerative neutrophils with intracellular and extracellular cocci and/or peanut shaped purple shaped yeast organisms.⁷ The recommended tape is Scotch 3M Gloss Finish, Multitask Tape. Collect your sample and the stain the tape with Diff Quik (omitting the alcohol dip), press onto a glass slide and read using a microscope. Acetate tape preps can also be used to identify Chorioptes bovis,^{6,7,14}

Direct Examination of Hairs

Hair sampling to evaluate for dermatophytes is performed by plucking affected hairs with hemostat, place on slide and apply 1-2 drops of a clearing agent-(10% Potassium hydroxide (KOH) solution, and apply a cover slip. Warm the slide for 15-20 minutes, and evaluate hair shafts. First, under 4X evaluate hairs, infected hair will appear pale and swollen. Second, re-examine under 40X for arthrospores within the hair shaft; these will appear as small clear bubbles in the hair shaft.^{4,18} This is difficult as well as time consuming and will take awhile to become experienced with this technique.

Dermatophyte Test Media (DTM culture)

When obtaining hair and crusts samples for a dermatophyte culture one must add few drops of niacin (Vitamin B complex) to all DTM's to satisfy the growth requirements of Trichophyton equinum, regardless of in-house culture or sending to laboratory. When preparing the site to take a culture, the use of Isopropyl Alcohol to cleanse the hairs of saprophytic (clinically irrelevant) fungi. It is very important to allow the alcohol to dry prior to collection or you may experience a false negative result. Dermatophyte Test Media (DTM) will suppress growth of saprophytes and contaminant bacteria because it contains

chlorotetracycline, gentamycin, and cyclohexamide.^{4,18,19} There is a phenol red pH indicator also included within the media. Dermatophytes use protein first, creating alkaline metabolites and red color change concurrently with colony growth. False-positive color changes occur, when saprophytes have exhausted the carbohydrate source on the plate, they will then utilize protein and cause a late red color change.¹⁸ False-negatives occur (rarely). Once you identify the red color change concurrent with colony growth, microscopic examination is important to confirm your diagnosis. The procedure is as follows: Typically 7-10 days of growth on the media is required before macroconidia are visualized. Use clear cellophane tape and press lightly onto your colony within the DTM. Then apply 1-2 drops lactophenol cotton blue.¹⁹ You may examine immediately under your microscope at 40X. If there are no macroconidia visible, wait a few days for the colony to mature and re-examine.

Dermatophilosis congolensis Preparation

Place 1-2 drops of saline on a clean slide. Clip off excess hair from the crust sample and place crust into saline. Allow sample to macerate/soften for 15 minutes and then remove larger pieces. Crush out the remaining material on the slide and allow to air dry. Heat fix slide for a few seconds. Stain with Diff Quik or methylene blue. Allow to dry and examine under microscope 100X oil and with immersion you should visualize cocci shaped bacteria in a "railroad track" orientation.^{4,19}

Biopsy

Biopsy should be considered if immune mediated disorders or neoplastic conditions are suspected. Consideration of these differentials is also recommended when treatment has been pursued and failures or relapses have occurred.¹⁹ In most cases, especially a suspected PLV, skin biopsies should be read out by a dermatohistopathologist with an interest in equine skin diseases.⁷ Acute changes including leukocytoclastic vasculitis, thrombosis and vessel wall necrosis are often scarce and can easily be overlooked, and when present may provide a diagnosis.^{5,7} Vessel wall thickening and hyalinization, along with epidermal hyperplasia or papillomatous, may be detected in chronic lesions. If secondary bacterial infection is severe, it is recommended to clear this before taking the biopsy.¹⁹

Biopsy for Culture

This may be necessary if bacterial or fungal infection is suspected or not responding to appropriate therapy.¹⁴ When collecting a biopsy for culture it is important to clip the hair and scrub the superficial area as if you were to perform a surgical procedure. The biopsy is taken as sterile precautions are maintained and the sample placed in a sterile cup or sterile media. This should be sent to the lab as soon as possible. Otherwise, superficial contamination will compromise your results.

Complete Blood Count and Chemistry Panel

This may useful in helping to rule out hepatogenous photosensitization disorders & other metabolic illnesses.⁷

Future Genetic Screening Tests

Mittman et al have identified quantitative trait loci (QTL) for CPL in 917 German draft horses. Thirty-one paternal half-sibling families comprising 378 horses from the breeds Rhenish German, Schleswig, Saxon-Thuringian (ECA9, 16, 17), and South German (ECA1,7) were recorded.^{19a} This is an important step toward the generation of a screening test.

MEDICAL TREATMENTS

Choosing the appropriate therapy involves recognition and identification of predisposing, perpetuating and primary factors.⁷

Environment

Recommendations include considering if the environment is contributing to a primary underlying problem.

(1) Pastures and paddocks with mud, water or sand can predispose, and worsen the condition (i.e. Arabian horses and sand).^{1,6,7}

(2) Keep horses in clean dry stalls during wet weather.

(3) Do not release horses into pasture until the morning dew has dried.^{6,7}

(4) If you suspect contact allergic (affecting all pasterns), suggest alternate source of bedding (the treated or aromatic types of wood shavings contain chemicals that can cause contact hypersensitivity).^{1,6,7,11}

(5) If a horse has heavy hair feathers or has involvement around the ergot and at the back of the fetlock joint, clip feathers over the pasterns to decrease moisture retention.^{1,6,7}

(6) If you suspect PLV, avoid UV light exposure with stabling or wraps.^{6,7,15,16}

(7) Daily cleansing of the affected skin immediately after exercise while the sweat is still present using an antiseptic shampoo (e.g. chlorhexidine).^{16a}

(8) If lesions are located beneath the saddle, barrier creams prior to exercise, toweling or cotton sheet, which is washed and changed daily may prevent further exacerbation of lesions.^{16a}

(9) Lesions on the shoulders, blanket and saddle pad contact zones should have a clean cotton or synthetic sheet as a barrier that can be washed on a regular basis.

Clinical Management - Topical Therapy Antibacterial

In EPD secondary bacterial infections with Staphylococcus spp. are often a common problem that often complicates the diagnosis.^{1,2,5,7} The antibacterial shampoos available are Benzoyl Peroxide 2%, Ethyl Lactate, or Chlorhexidine 2%. Shampoo area 1-2 times daily, lather, leave on 10 minutes, rinse and dry well.^{2,4,5,7} This should be done for 7-10 days, then to 2-3 times weekly. Another topical agent gaining increased use in both the human and veterinary field is Accelerated Hydrogen Peroxide (PURE OXYGEN®). This product can be applied to horses as a fungal wash/rinse or sprayed on and left to drip dry. It has an excellent spectrum of activity against various bacterial, fungal and viral pathogens (www.anivacfirst.com; www.virox.com) and is safe for use on all horses and surfaces.

Regardless of which topical agent is chosen, protection of the affected pastern(s) is imperative. Dry environment without bandaging is the most effective treatment. Some dermatologists recommend using a padded, water repellent bandage (changed q 24-48 hours). Facilitator® (Blue Ridge Pharmaceuticals) is a hydroxyethylated amylopectin liquid bandage which has been used successfully by some when applied every 1-3 days after cleansing^{-2,7} If lesions are exudative, astringents solutions, such as lime sulfur or aluminum acetate solution can be used. These agents will cause drying to the area and less exudation. Topical ointments are available for treating localized bacterial infections. Silver sulfadiazine and 2% mupirocin ointment both have excellent penetration into the epidermis and can be used for both dermatophilosis or staph bacterial infections.² Clipping and cleansing is paramount to success with any ointment.

Two recently studied additions to the topical armamentarium include Mudstop® and kunzea ambigua oil (Greasy Heal KO®, Xderma). Ten of 11 cases treated with a Mud Stop (antibacterial agents and humectants -agents that lower water activity) revealed significant improvement.^{16b} In a RDBPC study, 7 days of kunzea oil topically resulted in complete resolution 7/11 treated patients. Kunzea oil contains various active constituents such as pinene, 1-8-cineole (eucalyptol), and sesquiterpene alcohols. It is supplied as an ointment (20%) along with salicylic acid (50 g/kg) and reported to kill Staphylococcus aureus and various other gram-positive organisms, as well as yeasts and dermatophytes.^{16c}

Antifungal

Lime sulfur dips and spray can be used for localized treatment of the pastern for dermatophytes and mites. Enilconazole labeled for use in horses in many countries other than the United States and is used to treat fungal infections with good success.^{2,7} Miconazole shampoo 1% or shampoo that contains miconazole 1% and chlorohexadine can be used.

Steroids

Topical steroids can be used for immune mediated conditions such as pastern leukocytoclastic vasculitis. Triamcinolone spray 0.015% and hydrocortisone 1% leave on conditioner can be used in conjunction with systemic immunomodulators to treat this disease. In addition, good success has been noted with topical betamethasone 1% or aclometasone 0.05% applied to the lesion.² The author has recently had good success using mometasone (Mometamax®) to treat PLV patients as part of a study protocol.

Systemic Therapy Antibiotic Medications

The most common antibiotic used in the horse is Trimethoprin Sulfa (15-30 mg/kg). If the bacterial infection is severe, a 3 week course may be necessary, often in conjunction with topical antibacterial shampoos.^{2,4,7,14} Monitor closely for signs of colitis/diarrhea and discontinue immediately if noted. Enrofloxacin 5 mg/ kg of injectable orally every 24 hours has been used with success.^{2,7} This drug should never be use in foals and growing horses. Procaine penicillin G -22,000 IU/kg IM BID 7-10days continues to be a reasonably priced injectable option for dermatophilosis.

Antifungal Medications

Systemic antifungal therapy is often unnecessary in the horse. Griseofulvin powder is available for the horse. However, there has been no pharmacokinetic data published and the efficacy is questionable.^{6,18} Ketoconazole, itraconazole and fluconazole are effective for the systemic treatment of dermatophytosis in humans, cats and dogs. These agents are not currently approved for use in horses in the United States.¹⁸ Ketoconazole (30mg/kg) has very low absorption (23%) from the gastrointestional tract in horses and can be very expensive.²⁰ In addition, itraconazole and fluconazole can be used. Recommended dose for itraconazole is $5\neg10 \text{ mg/kg}$.^{27,18,21} One published report using fluconazole in the horse recommends a loading dose of 14mg/kg/day, then 5 mg/kg/day can be used safely.²² The cost of these medications limits their use.

Immunosuppressive/ Immunomodulary Therapy

Immune mediated conditions such as pastern leukocytoclastic vasculitis may need to be treated with immunosuppressive doses of steroids as well as decrease the exposure to UV light.^{2,5,7} Typically, dexamethasone, 0.1-0.2 mg/kg every 24 hours for 7-14 days, then taper slowly over the next 4-6 weeks.^{2,7} Prednisolone or prednisone 2mg/kg every 24 hours can be used as well.^{2,7} Pentoxifylline, 8-10 mg/kg PO, has immunomodulating properties such as inhibition of TNF- α , IL-1 and IL-6. This drug has as been reported to be successful in a few cases. It is a phosphodiesterase inhibitor that increases red blood cell deformability and platelet aggregation, therefore inhibiting thrombosis. In addition it influences leukocyte deformability and migration.^{2,3} Long term control can often be achieved using topical steroids and or Pentoxifylline once the lesions are under control. A RDBPC study looking at the efficacy of pentoxifylline (Navicon®) for treatment of PLV along with topical Mometamax® is yielding promising results. (Personal data)

Anti-Parasitic Therapy

Ivermectin (1% solution)-Give 300 mcg/kg PO weekly for 4 doses.^{2,7,4,17} May need to repeat and treatment failures can occur as these mites are surface feeders. A recent study in 19 horses looking at oral moxidectin (0.4 mg/kg body weight) given twice 3 weeks apart in combination with environmental treatment with 4-chloro-3-methylphenol and propoxur failed to yield positive results.²⁴

Although topical treatments are labor intensive, they are currently the most effective. All contact animals as well as affected horses should be treated. Topical organophosphates such as malathion (0.5%) and coumaphos (0.06%) or topical permethrin can be effective. Some authors suggest selenium sulfide shampoo followed by lime sulfur (6 ounces/gallon), sponged on every 5 days for 1 month.^{4,7,17} Fipronil spray 0.25% has been shown to be effective against Chorioptes bovis in one study.¹⁴ These mites can live

off the host up to 70 days, so environmental decontamination is important, including barn, stalls and bedding, tack and grooming equipment.

CONCLUSION

The prognosis of EPD depends on the underlying cause is and ability to identify it and the chronicity of the condition. Ensuring that predisposing, primary and perpetuating factors are taken into consideration during your diagnostic work-up and treatment plan will optimize a positive outcome.

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NOTES



ON THE OUTSIDE OF THE HORSE LOOKING IN: SKIN MEETS EQUINE MEDICINE

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INTRODUCTION

The dermatological manifestations of systemic disease are not always recognized. They may be subtle and appear initially similar to other unrelated superficial disease processes leading to misdiagnosis. Detection of systemic disease involvement relies upon a complete evaluation of the patient, which should include a thorough physical examination, relevant clinical pathological investigation and appropriate dermatological analysis. This presentation seeks to present systemic medical conditions which may have dermatological manifestation as their primary or only superficial manifestation.

IMMUNE MEDIATED CONDITIONS

Purpura hemorrhagica

This condition is a non-thrombocytopenic vasculitis syndrome that chiefly affects the distal limbs and ventrum of the horse. Purpura hemorrhagica is classically associated with exposure to or infection with *Streptococcus equi* subspecies *equi* (*S. equi*), the bacterial causative agent of Strangles. The resulting immune complexes circulate and lead to the onset of vasculitis. Deposition of complement near these immune complexes situated on the vessel walls results in cell membrane destruction and cell death. Other bacterial or viral agents including Equine Infectious Anemia (EIA), *Cornyebacterium pseudotuberculosis* and *Rhodococcus equi* can cause a similar syndrome. Vasculitis may also occur following exposure to vaccinal antigens, especially those directed against *S. equi*. Affected horses have swelling of affected tissues and regional sloughing of skin in more severe cases. Other clinical signs include fever, anorexia, weight loss, synovitis, tenosynovitis reluctance to move, and lethargy. Signs of colic may occur, and petechiation of mucous membranes may be present. Areas of vasculitis are hot and painful to touch. Lameness results from pain associated with tissue movement and some cases develop profound laminitis.

Diagnosis is based on the characteristic clinical signs and a recent history of potential exposure to *S. equi* or vaccination. Serological assay of serum antibodies to the *S. equi* M protein (SeM) may suggest exposure in cases where none was known. Skin biopsies demonstrate a leukoclastic vasculitis. Differential diagnoses include contact allergy, photosensitivity, and severe ulcerative pyoderma.

Treatment is centered on control of vasculitis. Goals of treatment include removal of the antigenic stimulus, reduction of the immune response, amelioration of inflammation, and provision of supportive care. Corticosteroids are the mainstay of treatment with high doses (dexamethasone 0.1-0.2mg/kg IV or IM for 3-5 days) required in the initial phases of treatment, with subsequent tapering of dosage over time as control is achieved. Prolonged courses of treatment (up to three weeks) may be necessary. Recurrence of clinical signs may occur with decreasing corticosteroid dose. In such cases additional increased doses may be required to regain control. Prednisolone may also be used but is considered not as effective for gaining control in the initial stages of the condition. In addition to systemic corticosteroids, topical anti-inflammatories are recommended in situations where they are tolerated. Antimicrobial coverage is also prudent, with systemic penicillin the first choice. This is aimed at resolving any precipitating foci of Streptococcal infection as well as controlling contamination of denuded areas post sloughing.

Prognosis is good in cases that response rapidly to corticosteroid treatment. Relapse during treatment is a negative indicator. It is imperative to avoid vaccination of previously affected horses with preparations containing Streptococcal antigens as fulminant disease can occur.

Infarctive purpura hemorrhagica

Infarctive purpura hemorrhagica is a condition resulting from extension of vasculitis to multiple tissues and organ systems, resulting in infarction that may affect the kidneys, heart and the skeletal muscle.¹ In addition to the cutaneous signs noted above, profound regional or generalized muscle swelling, and significant apparent abdominal discomfort can occur. Acute muscle atrophy is also reported.²

Diagnosis is based on clinical appearance and elimination of other causes of myositis. A widebased stance and reluctance to move are characteristic. Ultrasonography of the affected musculature shows pockets of edema within the muscle body. Clinical pathology reveals a neutrophilia with a left shift, hyperfibrinogenemia in advanced cases, hypoalbuminemia, and markedly elevated creatine kinase (CK) and aspartate aminotransferase (AST) activity. Serology indicates a high or rising SeM titer. Muscle biopsy shows acute coagulative necrosis of affected areas in contrast to a lack of pathological findings in palpably normal areas. Differential diagnoses include exertional rhabdomyolysis and acute exacerbation of underlying nutritional myopathies.

Treatment includes high doses for prolonged periods of anti-inflammatory corticosteroids, antimicrobials directed against suspected *S. equi* infection, non-steroidal anti-inflammatory drugs (NSAID), and generalized supportive care. Myositis may lead to profound myoglobulin release from damaged muscle tissue therefore intravenous fluid therapy to promote diuresis and minimize potential for myoglobinuric nephrosis is prudent.

Prognosis is guarded. In addition to skeletal muscle lesions, myositis and infarction of the lungs and myocardium can occur.³

Alloimmune thromobcytopenia

In addition to the commonly recognized colostrum associated syndrome of neonatal isoerythrolysis (NI), neonatal foals may also suffer from an alloimmune thrombocytopenia.⁴ Cutaneous manifestations may occur, appearing as crusting and scabbing of the skin. Prominent petechiae and ecchymoses of the mucous membranes and conjunctiva may be present leading to large areas of hemorrhage and ulceration.

Diagnosis is achieved by the elimination of other causes of profound thrombocytopenia. No other abnormalities of hemostasis are present. Assay of platelet associated antibodies is useful in support of the diagnosis.

Treatment consists of anti-inflammatory doses of corticosteroids, broad spectrum antimicrobial coverage, topical treatment of affected areas, and supportive care which may include provision of alternate nutrition in the presence of nasolabial, oral and lingual mucosal involvement.

Prognosis is favorable with prompt identification of thrombocytopenia as affected oral areas heal rapidly once thrombocytopenia is managed. Complications relate to introduction of sepsis to devitalized cutaneous areas or generalized depression from inadequate nutritional intake.

Cutaneous equine sarcoidosis

Cutaneous equine sarcoidosis (CES) is one of the equine idiopathic granulomatous diseases (IGD). A number of other names are given to this condition, including systemic granulomatous disease and equine histiocytic dermatitis. This is a rare condition of horses manifest as cutaneous scaling and crusting.^{5, 6} No underlying cause or mechanism has been discovered. An analogous condition in humans has similar histopathology and is thought to be an aberrant antigenic reaction. In addition to the cutaneous signs, affected horses may display fever, weight loss, anorexia, respiratory distress, peripheral lymphadenopathy, and exercise intolerance.

Other organ systems involved in the horse display a similar histological pattern to affected skin. Granulomatous pneumonia and granulomatous enteritis have been reported.^{7,8} In a review of nine horses with CES, skin lesions were found on horses with GE and GP, and 5 of 9 CES cases also had lung involvement.⁹

Diagnosis is based on history and clinical presentation. Blood work reveals a neutrophilia, hyperfibrinogenemia and hyperproteinemia consistent with inflammation. Culture of lesions is usually negative. Skin biopsies mid-dermal sarcoid type granulomas with many histiocytic cells, superficial dermal infiltrate of multinucleated histiocytic giant cells, and a smaller number of superficial dermal neutrophils, lymphocytes, and plasma cells.^{7, 8} Differential diagnosis includes dermatophilosis, dermatophytosis, pemphigus foliaceus, and drug eruptions.

Treatment is based on the use of immunosuppressive doses of corticosteroids. Prednisolone (2–4 mg/kg daily) or dexamethasone (0.1–0.2 mg/kg daily) for 1-2 weeks followed by a tapering dosage once improvement is noted forms the mainstay of therapy. Parenteral dosage may be more effective in cases suffering from malabsorption. Broad spectrum antimicrobial coverage may be beneficial in cases with generalized lesions. Additional therapies reported include azathioprine and pentoxifylline.

Prognosis is poor in horses with internal organ involvement as generalized devitalization due to malabsorption may progress. In horses with cutaneous involvement only prognosis is better.

Multisystemic eosinophilic epitheliotropic disease (MEED)

This condition is similar granulomatous conditions however the predominant infiltrating cell type is the eosinophil.⁷ In addition skin lesions that are ulcerative and nodular, the submucosal layer of the intestinal tract is also affected. The coronary bands may be involved leading to lameness. An inappropriate response to antigen is suspected as the cause of this condition.

Diagnosis is by demonstration of eosinophilic infiltration of biopsy samples (skin, intestine). Treatment consists of high dose and long term corticosteroids. Transient improvement with treatment can occur, although long term prognosis is poor.

SYSTEMIC DISEASE

Pituitary pars intermedia dysfunction (PPID)

Also known as Cushing's disease, in horses this condition is almost exclusively attributed to hyperplasia or adenoma formation in the pituitary pars intermedia, therefore PPID is the preferred term for the disorder.¹⁰ In the normal horse hypothalamic dopaminergic neurons exert an inhibitory effect on production of pro-opiomelanocortin (POMC) by pituitary pars intermedia cells. Loss of this inhibition allows proliferation of pars intermedia melanotropes and excessive production of POMC-derived peptides including adrenocoticotropin (ACTH). All breeds and types of equids can be affected with PPID, however there appears to be a greater risk in Morgan horses and ponies. No gender bias occurs, and age of onset is typically over 18 years of age however much younger cases have been documented. There is no gender predilection and age of onset of clinical signs is generally 18 to 23 years, but cases as young as 7 years have been reported.

The clinical sign most often ascribed to PPID in horses is hirsutism. Hyperhidrosis is also present in approximately two-thirds of horses with PPID. Weight loss, lethargy, and chronic secondary infections can occur. Laminitis is the most serious condition reported, with up to half of all PPID horses affected.

Diagnosis is presumptively suggested by the characteristic clinical signs, however covert disease is commonplace early in the clinical progression. Abnormal laboratory values may include mild anemia, neutrophilia, and lymphopenia. Hyperglycemia, elevated liver enzyme activities, hypercholesterolemia, and hypertriglyceridemia are reported. Definitive diagnosis is challenging, with baseline ACTH levels unreliable. The overnight dexamethasone suppression test appears more reliable for detection of disease, as does the more recent TRH-stimulation test.

Treatment of equids with PPID is centered on improvements in general health care along with a variety of management changes to improve the condition of older animals. In the earlier stages of PPID, management changes, including body clipping, correction of dental abnormalities, and improved nutrition, may be the only action needed. Medications used to treat equids with PPID include serotonin antagonists (cyproheptadine) and the dopamine agonist pergolide mesylate. Prascend® (Boehringer Ingelheim) is the only FDA approved form of pergolide mesylate and is produced a 1mg tablet. Dose is 0.002 mg/kg PO q24 hours (1 mg/d for a 500 kg horse).

Secondary (hepatogenous) photosensitization

Phylloerythrin is a porphyrin compound formed by microbial degradation of chlorophyll in the gut. It is normally conjugated in the liver and excreted in the bile. If the liver is compromised and cholestasis occurs, phylloerythrin accumulates in the blood and circulates allowing exposure to ultraviolet light. Oxidative injury to the blood vessels and skin results. Pyrrolizidine alkaloid is the most important causative agent, however numerous plants and toxins can precipitate photosensitization.

Diagnosis is by the characteristic lesions in depigmented areas and concurrent evidence both clinical and clinicopathological of hepatic compromise.

Treatment is based on removal of the precipitating agent from the diet, reducing exposure to sunlight, managing hepatic compromise, and treatment of the skin lesions.

Prognosis depends on the extent of skin loss and severity of the underlying hepatic disease.

Cutaneous infarction

Bacterial sepsis may cause inappropriate activation of the clotting cascade which can lead to infarction of cutaneous vessels.¹¹ Avascular necrosis and sloughing can result. Diagnosis is aided by finding areas of skin that appear discolored with mild swelling and hypothermia present. Cutaneous sensation is absent, and there is no ability to elicit local hemorrhage. In the author's experience, distal limbs are predominantly affected. Extensive tissue areas and multiple organs may rapidly become involved as the condition progresses. Prognosis is grave in cases with extensive involvement.

NEOPLASIA

Cutaneous lymphoma

Primary skin neoplasms do occur or there may be direct spread for subcutaneous tissues. Lymphosarcoma is the most common disseminated neoplasia to affect the skin, in addition to involvement of lymph nodes and the intestinal tract. Epitheliotropic lymphoma, mycosis fungoides, is a T-cell origin condition.¹² Widespread crusting, scaling, ulceration can be seen, with varying degrees of pruritis. Prognosis is poor.

Non-epitheliotropic lymphomas may be seen as subcutaneous nodules that wax and wane in severity. Prognosis is better compared to epitheliotropic conditions or those with multi-organ involvement. This is considered a T-cell rich large B-cell lymphoma. Response to corticosteroids is favorable, and spontaneous remission has been reported.

PARANEOPLASTIC CONDITIONS

Lymphoma may not have direct epithelial involvement, but may by manifest as a paraneoplastic syndrome with intermittent fever, alopecia, crusting and pruritis.^{13, 14} Other organ system involvement has also been reported.¹⁵ Cytotoxic T lymphocytes are considered to have a role in the pathogenesis of this syndrome.¹⁶ Histological findings may be diverse.

CONGENITAL

Lethal white foal

This is a well-recognized autosomal recessive disorder of white foals.¹⁷ The vast majority of affected foals have been of the Paint breed, however Quarter Horse, Thoroughbred, and Miniature Horse foals have also been reported. Foals are typically completely white and may have nonpigmented irises. The conditions is inherited as an autosomal recessive trait when both parents are carriers of the Ile118Lys mutation of endothelin-B receptor protein. The condition occurs in foals from breeding of Paint horses with the overo coat color pattern, especially when both parents display frame overo. Within 12 to 24 hours following birth all develop profound abdominal distension and colic. Occasional all white foals are born without the condition so a confirmed diagnosis is required before euthanasia.

The white coat is due to lack of melanocytes in the skin, and intestinal obstruction results from a congenital intestinal aganglionosis (an absence of submucosal and myenteric innervation). Although surgical intervention has been reported the condition is uniformly fatal.¹⁷

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NOTES



NUTRITIONAL ASSESSMENT OF HOMEMADE AND RAW DIETS What Foods These Morsels Be

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Recently, the American Animal Hospital Association released the Guidelines for Nutritional Assessment (July/August JAAHA 2010). Utilizing the two-step iterative process, a **screening assessment** is made and if concerns are found, then a more **detailed assessment** is made. Following assessment, data are analyzed, a plan formulated and initiated, and repeated evaluation and modification of the plan is made. The importance of nutrition is emphasized by it being considered one of the "5VA's" (5 vital assessments): temperature, cardiac function, respiratory health, pain, and nutrition (http://www.everypeteverytime.com/index.html).

The American College of Veterinary Nutrition recommends a two-step process in making nutritional recommendations. The process is iterative in that it should be re-evaluated periodically and changes made as deemed necessary.

The first step is **ASSESSMENT**. During this step, assess the **ANIMAL**, the **DIET**, and the **FEEDING** factors.

ANIMAL FACTORS assessed include gathering historical information, performing physical examination, body condition scoring, and evaluating laboratory and imaging results if indicated. Gather information on any health or disease-related conditions, medications (including over-the-counter and nutraceuticals/supplements), reason for visit, and other household members. A thorough physical examination is performed and a body condition score assigned. There are 5- and 9- point body condition scoring systems; either can be used. In either scale, the middle number of the scale (3 out of 5 or 5 out of 9) represents ideal body condition and a body fat content of 15-25%; numbers lower than this correspond to lower body condition and less body fat (0-15%) while numbers higher than this correspond to higher body condition and greater body fat 3(5%). Assigning a body condition score provides more information than body weight alone and can be used with a muscle condition scoring system where 3 = adequate muscle mass, 2 = decreased muscle mass, and 1 = severe muscle wasting (sarcopenia).

DIETARY FACTORS include gathering information on dietary intake and inspection of the food, if needed. Take the dietary history from the person that actually feeds the pet(s) asking for type of food, amount fed, frequency of feeding, table food or treats, access to other food (garbage, outside, etc), supplements, and medications (including over-the-counter). If necessary, inspect a sample of the food or send a sample for analysis (i.e. Cornell Animal Health Diagnostic Center, Woodson Tenent Laboratories, EMSL Food and Consumer Products Testing Lab, etc). Pet foods can be purchased in a variety of forms – dry, canned, semi-moist, semi-dry, liquid, and frozen.

Reading the food label is also beneficial. The food label can be roughly divided into a principal display panel and an information panel. The **PRINCIPAL DISPLAY PANEL** contains information directed towards the consumer including the product name, species for which the food is intended, net weight of product, and descriptive words and/or pictures (e.g. "new and improved", picture of a famous cat, etc). The **INFORMATION PANEL** contains the important information including ingredient list, guaranteed analysis, feeding guidelines, contact information, and the nutritional adequacy statement. Although often maligned and not as complete as labels for human foods, there is useful information to be found. Ingredients are listed in descending order according to pre-processing weight and names are set by AAFCO (e.g. by-product, etc); this means that ingredients containing moisture that weigh more will be listed first. Unfortunately, this does not give information as to the quality or exact amount of each ingredient; also, different forms of the same type of ingredient are listed separately. Chemical sounding ingredients are typically vitamins, minerals, and preservatives. Feeding guidelines are provided that are suitable for most, but not all, dogs or cats that consume the diet. The manufacturer's or distributer's name and address is required and questions regarding the food should be directed to them; they should be able

and willing to provide answers.

When contacting them, several questions should be asked:

- 1. Do you have a Veterinary Nutritionist or some equivalent on staff in your company? Are they available for consultation or questions?
- 2. Who formulates your diets and what are their credentials?
- 3. Which of your diet(s) is AAFCO Feed Trial tested? Which of your diets have been AAFCO Nutritional analyzed?
- 4. What specific quality control measures do you use to assure the consistency and quality of your product line?
- 5. Where are your diets produced and manufactured? Can this plant be visited?
- 6. Can you provide a complete product nutrient analysis of your bestselling canine and feline pet food including digestibility values?
- 7. Can you give me the caloric value per can or cup of your diets?

The **guaranteed analysis** provides information regarding the 4 major components of a pet food as percentages of the diet as fed including minimum amount of crude protein, minimum amount of crude fat, maximum amount of crude fiber, and maximum amount of moisture. "Crude" refers to the analytical procedure and does not refer to the quality of the ingredient.

The **nutritional adequacy** statement must be included and is designed to ensure that the product, when fed as the sole source of nutrition, is complete and balanced for one or more life stages, including how this adequacy was verified. The four recognized life stages by AAFCO are pregnancy, lactation, growth, and adult maintenance, and nutritional adequacy can be determined by feeding trials or by calculation. The calculation method involves determining the amount of nutrients in the diet and comparing to AAFCO nutrient profiles for that/those life stage(s). Feeding trials are performed by feeding the diet to the animals in that/those life stage(s) following AAFCO protocol. Feeding trials, while not perfect, provide indirectly information on bioavailability of nutrients and is preferred method for validation of nutritional adequacy. Therapeutic diets, supplements, and treats often do not carry a nutritional adequacy statement. Therapeutic diets are formulated for specific non-healthy conditions, which are not recognized by AAFCO and for which no nutrient profiles exist (e.g. renal failure, liver failure, etc); they usually carry a statement such as "intended for intermittent use" or "use only under the supervision or direction of a veterinarian". Snacks and treats are not formulated or intended to be the sole source of nutrition; therefore, they are not required to carry a nutritional adequacy statement.

The label often contains other information, much of which do not have official definitions. According to AAFCO, "natural" is "...only acceptable in reference to the product as a whole when all of the ingredients and components of ingredients meet the definition....the use of 'natural' is false and misleading if any chemically synthesized ingredients are present in the product; however, AAFCO recommends that exceptions be made in the cases when chemically synthesized vitamins, minerals, or other trace nutrients are present as ingredients in the product, provided that the product is not a dietary supplement and that a disclaimer is used to inform the consumer that the vitamins, minerals, or other trace minerals are not natural. For example, 'Natural with added vitamins, minerals, and other trace minerals." AAFCO defines "natural" as "a feed or ingredient derived solely from plant, animal, or mixed sources, either in its unprocessed state or having been subject to physical processing, heat processing, rendering, purification, extraction, hydrolysis, enzymolysis, or fermentation, but not having been produced by or subject to a chemically synthetic process and not containing any additives or processing aids that are chemically synthetic except in amounts as might occur unavoidably in good manufacturing processes." "Organic" does not have a specific AAFCO definition other than in reference to processing, "organic (process): a formula or a specific ingredient within a formula feed that has been produced and handled in compliance with the requirements of the USDA national Organic Program (7 CFR Part 205)." The USDA National Organic Program (NOP) "develops, implements, and administers national production, handling, and labeling standards for organic agricultural products. The NOP also accredits the certifying agents (foreign and domestic) who inspect organic production and handling operations to certify that they

meet USDA standards." "Human grade" ingredient has no official definition and can be interpreted differently by different people; there are no standards by which to define or interpret this wording. Other designators such as "premium" and "gourmet" also have no official definitions. Such designators are arbitrary and subject to interpretation.

HOMEMADE DIETS

Some owners prefer to prepare homemade foods – feel less guilty and have impression of preparing a "real meal" that is "more natural" and "more traditional". Nearly all dogs and cats in the US consume table foods at some time in their lives. Majority of dogs and cats in US receive >90% of calories from commercial foods. When a client wants to prepare pet foods at home, it is important for veterinarians to understand the client's reasons and motivation. In many cases it is possible to address their concerns and to recommend an appropriate commercial food. If they still wish to cook, then proper guidance can be provided. Some owners wish to cook homemade diets in order to provide a natural or organic food. Remember, there is no legal definition for the terms "natural" and "organic". Pet owners may also want to prepare vegetarian food for their dog or cat because they are vegetarian or vegan. Because cats are true carnivores, vegetarian cooking should be discouraged. Other owners wish to prepare homemade diets in order to avoid additives, preservatives, and contaminants. Pet food labels may be difficult to read and understand and they do not contain as much information as human food labels; therefore, some choose to home cook because they are more comfortable with being in control. Some pets will only eat table foods because it has become a habit. Lastly, homemade diets may be used for dietary elimination trials.

It is possible to achieve the same nutrient balance with a homemade food as with a commercially prepared food. However, this largely depends on the accuracy and competence of the person formulating the food, and on the compliance and discipline of the owner. Unfortunately, some homemade recipes are flawed even when followed exactly and consistently. In one survey, 90% of homemade elimination diets prescribed by 116 veterinarians in North America were not nutritionally adequate for adult dog or cat maintenance. Few of the recipes available in books, magazines, and on-line have been tested to document the nutritional adequacy of the diet. There are common nutrient problems in many homemade foods. Many formulations contain excessive protein, but are deficient in calories, calcium, vitamins, and microminerals. Commonly used meat and carbohydrate sources contain more phosphorous than calcium resulting in inverse calcium: phosphorous ratio. Foods designed by clients are commonly deficient in fat and energy density or contain an unpalatable fat source (vegetable oil). Homemade foods are rarely balanced for micro-minerals and vitamins because veterinary vitamin-mineral supplements are not complete nor are the nutrients well balanced within the product.

Veterinarians encounter a wide variety of pet food recipes from breeders and the popular press. Some owners want an opinion as to whether the recipe is good and others want to alter the recipe. Homemade formulations can be checked for nutritional adequacy and adjusted using the "quick check" guidelines:

- 1. Do five food groups appear in the recipe?
- 2. Is the carbohydrate source a cooked cereal and present in a higher or equal quantity than the meat source?
- 3. What is the type and quantity of the primary protein source?
- 4. Is the primary protein source lean or fatty?
- 5. Is a source of calcium and other minerals provided?
- 6. Is a source of vitamins and other nutrients provided?

Substitution of ingredients can be done, but should be researched as to the equivalent amounts. One protein source is not the same as another. Other instructions that should be given owners include those for preparation, storage, and feeding. Emphasis should be made to not eliminate an ingredient or indiscriminately substitute ingredients. Owners that wish to use raw eggs and meats should be informed that there is a risk for infectious diseases. Animal ingredients should be cooked for at least 10 minutes at 180F. Vegetable ingredients should be washed or rinsed and cooked if increased digestibility is desired. Since antioxidants are not usually added to homemade diets, storage in airtight containers at refrigeration

temperature can be done for 7 day stretches. Large quantities can be frozen. Owners should check appearance and odor daily to make sure rancidity or contamination has not occurred. Starches should be cooked to increase digestibility; however, they should be cooked separately from the protein source. Carbohydrate sources require a longer cooking time; meat and liver should not be overcooked or protein denaturation will occur

Pets should be evaluated routinely whether they are being fed commercial food or homemade food. Stools should be formed although they may contain more water. Body condition and weight should be maintained. If problems are encountered, then either the homemade diet should be re-evaluated and modified or use of a commercially available diet should be encouraged.

RAW FOOD DIETS (BIOLOGICALLY ACTIVE RAW FOODS)

Veterinarians deal with pet owners who have access to a large body of information on small animal nutrition. Food is something that everyone relates to because it is one of the necessities of life. Food can have important effects on psychological well-being. Diet is something that an owner can control. Nutritional therapy is viewed as natural and holistic as opposed to surgical and pharmacological management of disease. For these reasons, there are a growing number of homemade diet recipes available through the internet and published sources that tout health benefits.

An example of a non-traditional pet food is raw food diets. Proponents of raw food diets claim numerous benefits such as improvement in coat and skin; elimination of breath, body, and fecal odor; improvement in amount of energy and behavior; improvement in overall health and immune function; and reduction of the incidence of many medical conditions including allergies, arthritis, pancreatitis, and parasitism.

The rationale for use of raw food is simple. Dogs and cats are carnivores that evolved eating raw foods. In addition, commercial foods are heat processed which alters or destroys nutrients and essential enzymes. Therefore, commercial foods may not be a natural or nutritionally sound diet for dogs and cats.

Although there are numerous health claims for these diets, there is no scientifically proven information, only testimonials. There are several serious potential drawbacks.

- Nutritional imbalances. In one small study, raw food diets were found to have one or more of the following: an unbalanced calcium-to-phosphorous ratio, increased vitamin D levels, decreased potassium content, decreased manganese content, decreased or increased zinc content, decreased iron content, and increased vitamin E content.
- Intestinal foreign bodies. There are sporadic reports of esophageal foreign body and obstruction due to ingestion of bones.
- Infectious agents. Raw foods, especially meat, may contain infectious agents, many of which are • zoonotic. Escherichia coli O147:H7 was cultured from one homemade raw food diet. Raw pork may can contain Yersinia enterocolitica 4/0:3 and has been isolated from feces of dogs and cats fed raw pork. Listeria monocytogenes has also been isolated from raw pork and has been associated with disease in dogs including reproductive problems. Rendered raw meat has been shown to be contaminated with bacteria, including Salmonella spp, Proteus spp, and Pseudomonas spp, that may also be carried by flies. Clostridium difficile has been isolated from feces from dogs and cats. In addition to bacteria, raw foods may contain Toxoplasmosis, trichinella, and other parasites including Echinococcus. These may pose health hazards to animals as well as to the humans who are preparing the food. One argument given by raw food proponents is that the bacteria do not cause disease in dogs or cats. One concern that is often overlooked is the role of dogs and cats to be carriers of potentially zoonotic infectious agents. For example, dogs have been shown to carry Escherichia coli that can cause non-enteric Escherichia coli infections in human beings. In addition, indiscriminate use of antimicrobials may result in antimicrobial resistance of enteric organisms, which, in turn, may find its way into human medicine.

So what kind of recommendation do we make to clients? There are two issues that require resolving when dealing with raw food diets and clients who wish to feed them. First, we must decide whether we believe in their use and feel comfortable in providing advice concerning their use and

preparation. Second, we must provide competent advice on their use. These issues extend beyond health issues for dogs and cats to health issues with the human beings that share the same environment and prepare the food.

Nutrition consults

- The ACVN (<u>http://www.acvn.org</u>)
- Michigan State 517 / 432 7782
- North Carolina State 919 / 513 6871
- <u>http://www.cvm.ncsu.edu/vhc/vhwc/nutrition/</u> Ohio State 614 / 292 – 1221
- http://www.vet.ohio-state.edu/nssvet.htm
- Tufts University 08 / 839 5395 ext 84 696
- UC Davis 530 / 752 1387 <u>http://www.vmth.ucdavis.edu/vmth/services/nutrition/nutrition.html</u> http://www.ucvmc-sd.vetmed.ucdavis.edu/nutrition.cfm
- University of Missouri <u>http://www.vmth.missouri.edu/clin_nu.htm</u>
- University of Tennessee 865 / 974 8387 utvns@utk.edu
- Veterinary Information Network (<u>http://www.vin.com</u>)

FEEDING FACTORS to be assessed include how the nutrition is provided and must take into account owner and animal factors. Simply filling a bowl within reach of the animal is not enough; the appropriate diet must be provided in the appropriate amount. Obesity is the most common nutritional disorder of dogs and cats and, in part, is due to overfeeding. "One cup" of food refers to the amount of food contained in one 8-ounce measuring cup. Ask specifically for the size of the cup used and the size of the bowl that is filled up. Many owners feed free choice – "drive-by feeders" - without regard to amount. The amount of energy required by the pet can be determined using one of two formulae:

Linear: $[(30 \times BW_{kg}) + 70]$ Exponential: 70 x $(BW_{kg}^{0.75})$

This provides the **RESTING ENERGY REQUIREMENT** and this result is multiplied by a life stage or activity factor depending on the individual.

Factors used to estimate daily energy requirements					
Maintenance		Gestation			
I	ntact adult	1.8	First 42 days	1.8	
N	Veutered adult	1.6	Last 21 days	3.0	
C	Obese prone	1.4	Lactation	4.0-8.0	
V	Veight gain	1.2-1.4 at ideal	Growth		
V	Veight loss	1.0	Weaning to 4 mo	3.0	
C	Critical care	1.0	4 mo to adult	2.0	
Wor	k				
L	ight work	2.0			
N	Aoderate work	3.0			
H	Ieavy work	4.0-8.0			

Once the assessment is completed, the **ACTION** phase occurs where a plan is formulated and initiated involving type of diet, amount, frequency, etc. This is not the end of the process, however. Periodically, the patient and nutritional plan should be re-evaluated and adjusted as required.

NOTES



ADVERSE FOOD REACTIONS An Internist and Nutritionist Perspective

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An **adverse reaction to food** is defined as a clinically abnormal response attributed to an ingested food substance, and may be further categorized as immunologic or non-immunologic in nature. Food allergy is an immunologically mediated, reaction to ingested food. This is different than food intolerance, which is a nonimmunologically mediated adverse reaction including toxic reactions, pharmacological reactions, metabolic reactions, and idiosyncratic reactions.



ADVERSE REACTIONS AND FOOD HYPERSENSITIVITY.

Throughout life, animals are exposed to a great variety of potential dietary allergens. However, after a variable period of time, some animals may develop an immune response against a particular foodstuff that activates one or more immunopathogenic pathways. After development of this response, subsequent ingestion of this foodstuff results in clinical signs. These dietary antigens do not normally cause problems because the intestinal mucosa forms a barrier that limits absorption of macromolecules, but this mechanism is imperfect. There is evidence that antigens are absorbed through both normal and abnormal gut. Indeed, antibodies to food allergens, usually IgG, are often demonstrable in normal individuals, but they do not result in clinical disease. Upon initial presentation of the antigen to the gut mucosa, there is generally an immune response involving IgA. This reduces the amount of antigenic material that is absorbed. Immune complexes of antigen and IgA antibody are transported across hepatocytes, into bile, and re-circulated to the intestine. This local IgA response may be followed by a transitory systemic immune response, but immunologic tolerance follows. Thus, there is an apparent paradox of a vigorous local immune response followed by a systemic tolerance. Absorption of macromolecules can be altered in either direction by local immunity. Decreased uptake has been demonstrated experimentally following oral or parenteral immunization in rats, and increased absorption occurs in IgA-deficient human beings. Absorption is also enhanced by vasodilatation in the gut mucosa, such as that resulting from a local allergic reaction. In this case, the patient becomes caught in an immunological vicious circle because local hypersensitivity reactions favor access of allergens that in turn heightens the antibody response.

Factors that lead to development of hypersensitivity to ingested antigens are speculative. Those most frequently implicated are heat- and acid-stable glycoproteins with molecular weights of 18,000-30,000 Daltons. Hypersensitivity reactions involved in food allergies have been shown to involve types I, III, and IV reactions. Some studies indicate that IgE is implicated in some instances and the reactions involved include both the classic, immediate Type I reaction and the late-phase IgE-mediated reactions. The factors that determine the extent of absorption of allergens by the intestine are not fully understood, although local vasodilation is clearly facilitatory. Once local vasodilation is stimulated by local reactions, the cycle feeds on itself. What initiates the original immunologic reaction is not clear. Certainly, if clinical or subclinical gastrointestinal disease occurs which alters mucosal integrity, absorption of antigenic proteins may occur which may initiate the processes. Inflammatory mediators involved in food allergy may include interleukins, platelet activating factor, histamine and cytokines.

Clinical signs of food allergy relate primarily to dermatologic and gastrointestinal. Dermatologic signs often include pruritis, erythema, and secondary pyoderma. Gastrointestinal signs may include vomiting and/or diarrhea, flatulence, perianal fistulae, and anorexia. Other potentially associated

disorders include cholangiohepatitis/cholangitis, feline asthma, idiopathic epilepsy, and feline urinary tract disease.

Most basic food ingredients have potential to induce an allergic response, although proteins cause the majority of reactions. Dietary components reported to cause food sensitivity in dogs and cats include: cow's milk, beef, mutton, pork, chicken, rabbit, horse meat, fish, eggs, oatmeal, wheat, corn, soy, rice flour, potatoes, kidney beans, canned foods, cod liver oil, dry food, pet treats, and food additives.

Food intolerance is a non-immunological abnormal physiological response to a food item, and may involve, toxic, pharmacological, or metabolic reactions or dietary idiosyncrasies, in which the animal is unable to digest or otherwise process a dietary component. Examples of food intolerance include lactose intolerance, gluten intolerance, reaction to vasoactive amines in diet, reactions to histamine-containing foods or foods that stimulate histamine release, reactions to foods that contain opiates, food additives, and toxic reaction to food substances.

Treatment of food allergy

Elimination diets and dietary challenges. The most useful and reliable aid in diagnosis of dietary sensitivity is the procedure of feeding a restricted or elimination diet followed by dietary challenge with a test meal. Elimination diets must be individualized based on the previous dietary exposure. A detailed study of the animal's diet will allow identification of foods that have not been fed before, and that could be used to formulate a nutritionally balanced elimination diet that will "hypo-allergenic". If it is not possible to formulate a suitable elimination diet, then a restricted diet may be used that contains only one or two potential allergens, preferably ones that the animal has not eaten in the preceding month. Many homemade diets that are used as elimination diets are not complete and balanced (e.g. cottage cheese and rice, or chicken and rice). Supplementation with vitamins and minerals is encouraged, but avoid use of supplements that contain potentially offending foodstuffs (e. g. beef or pork). It is tempting to use commercially prepared "hypoallergenic diets" during the diagnostic period for owner convenience and to ensure feeding of a complete and balanced diet. This may be effective, but approximately 20% of dogs diagnosed as food hypersensitive when fed a home-cooked lamb and rice diet manifested clinical signs of allergic dermatitis when fed the commercially prepared lamb and rice diet. Gastrointestinal signs may subside in 3-5 days, but if it chronic in nature; it may take 4-6 weeks. Once clinical improvement is noted, it is advised to attempt to identify the offending antigen by introducing foodstuffs to the elimination diet

Protein hydrolysates. Because proteins with molecular weights over 18,000 Daltons are incriminated as being antigenic, modification of proteins to compounds having lower molecular weight may be of benefit. Protein modification is a process that alters the physical characteristics of protein molecules, presumably reducing the antigenicity and rendering them less able to elicit an immune response. By reducing the average weight of the protein molecule, this process can result in a protein that may be truly hypoallergenic. To be effective, it must reduce the molecular weight of the protein below 18,000 Daltons. Recently, several commercially available diets containing protein hydrolysates have been introduced including Exclude, DVM Pharmaceuticals, Hill's Prescription Diet z/d, and Purina's CNM HA-Formula. Anecdotally, these diets appear to be effective as elimination diets, and they have the advantage of being complete and balanced. These diets may be used long-term, but cost more.

Homemade and raw diets. Homemade diets allow promote control over ingredients and truly novel ingredient diets may be formulated. Because some dietary ingredients may become antigenic due to processing, feeding a whole ingredient or raw food diet means there is no processing. Additionally, homemade diets are typically more digestible and smaller quantities may be fed.

Management of food hypersensitivities. If the client has been cooperative, the presumptive food antigen has been identified. If this has occurred, or if it is not possible to identify the antigen, then long-term management procedures should be instituted. First, the diet is gradually changed from a home-prepared elimination diet to a commercially prepared diet of selected protein. This not only provides a nutritionally balanced and complete diet, but also is more convenient for owners. There are many single protein source diets available including diets that contain duck, venison, lamb, rabbit, and kangaroo. If

the animal continues to do well, it must be emphasized to the owner to not give table scraps or treats, and to not switch the diet even if clinical signs have not recurred.

Small intestinal bacterial overgrowth: This is characterized by finding a decreased B12 and increased folate concentration. Even without evidence of SIBO, there are dogs that respond to antibiotics, such as tylosin.

Immunosuppression

- Glucocorticoids either systemic (e.g. prednisone: 1-2 mg/kg PO q24h or divided q12h) or topical (e.g. budesonide: 3 mg/m² q24-48h (dogs), 1 mg/cat PO q24h (cats)). Glucocorticoids are often very effective if eosinophilic component.
- Azathioprine a purine analog that is immunosuppressive. Used primarily in dogs and has been reported that cats are very sensitive to toxicity. There may be a lag phase between initiation and response; however, newer data suggests that it is not necessarily more than 1 week or so. In dogs, there are a couple of protocols: 2 mg/kg PO q24h x 2-4weeks, then either 1 mg/kg PO q24h or 2 mg/kg PO q48h, then 1 mg/kg PO q48h until decide to stop. It can be used indefinitely if patient tolerates. May induce bone marrow suppression, liver disease, and pancreatitis
- Chlorambucil an alkylating agent also used as a chemotherapeutic drug. Dosages include: Dogs: 6 mg/m2 PO q48h for 2-4 weeks then taper or 0.25-0.33 mg/kg PO q72h for 2-4 weeks then taper; Cats: 2 mg/cat PO q48h for 2-4 weeks then taper or 2 mg/cat PO q72h for 2-4 weeks then taper. Can be myelosuppressive.
- Cyclosporin A inhibits T cell function; therefore, may be more effective with lymphocytic IBD. Dose: 5 mg/kg PO q24h. May be associated with renal and liver toxicity, myelotoxicity, and increased infections.
- Mycophenolate also a purine analog. Dosage: Dogs: 10-20 mg/kg PO q12h; Cats: 10 mg/kg PO q12h. Seems to be well tolerated. Main side effects are GI signs.
- Antimicrobial agents Recently, enteroinvasive E coli has been found in some boxers with ulcerative colitis. Enteroinvasive bacteria may play a role in other intestinal diseases. This may explain why some patients are "anti-microbial responsive" despite lack of evidence for SIBO. Tylosin: 10-20 mg/kg q 8 h for 21 days, 20-40 mg/kg q 12 h, tapered to lowest effective dose, 40-80 mg/kg/day po (cats). Metronidazole: 10-20 mg/kg q 12 h for 10-14 days, then q 24 h for 10-14 days; 10 mg/kg po q 12 h or 25 mg/kg/day po for 5 days (cats); Enrofloxacin: 10-20 mg/kg PO q24h; Oxytetracycline: 10-20 mg/kg q 8 h
- Vitamin B12 (cobalamin): patients with small intestinal disease even if not SIBO may have systemic B12 deficiency. With GI disease, oral replacement is not effective; therefore, parenteral therapy is required. Treatment includes: 1000 mcg SQ q 2-3 weeks, dogs/cats; Cats and dogs <5kg 250 mcg SQ q 7 days for 6 weeks, then q 2 weeks for 6 weeks, then q 4 weeks; Dogs 5-15 kg, 500 mcg/injection; Dogs > 15 kg, 1000mcg/injection
- Probiotics there are many probiotics available for use. Although some are "veterinary specific", there are not actually species specific probiotics. As a general rule: "more is better" more bugs of more types in more numbers. For comparison: VSL#3 has 450 billion organisms of 8 strains, Culturelle has 10 billion organisms of 1 strain, Proviable has 5 billion organisms of 7 strains, ProstoraMaxx has 100 million organisms of 1 strain, and Fortiflora has 10 million organisms of 1 strain. Probiotics may help with GI disease by altering the gut microflora, competing with pathogenic enteric organisms, and by producing beneficial substances while metabolizing potentially harmful ones.
- Anti-inflammatories sulfasalazine, which is salicylate bound to a sulfa antibiotic, is a good antiinflammatory agent for colitis. The bond prevents metabolism prior to entering the large bowel where bacteria cleave the bond releasing the salicylate to act locally. Sulfasalazine: 20-30 mg/kg q 8-12 h, 10-25 mg/kg q 8 h for 6 weeks, then taper; 10-20 mg/kg po q 8-24 h for up to 10 days (cats). Olsalazine: 10-15 mg/kg q 8-12 h, 5-10 mg/kg q 8 h for 6 weeks, then taper. Side-effects may include KCS due to the sulfa drug

- Omega-3 fatty acids exert anti-inflammatory effects by substituting into cell membranes where metabolism results in cytokines of the odd series. The dose is based on the amount of EPA and DHA in the product not the total amount of omega-3 fatty acids: 300 mg EPA + DHA per 10 pounds PO q24h.
- Motility modifiers Motility disorders occur with GI disease and modification of abnormal motility may help with diarrhea. These are typically opioids. Loperamide (Imodium): 0.1 0.2 mg/kg q8 12h PO (dog), 0.08 0.16 mg/kg q24h PO (cat cautiously); Diphenoxylate (Lomotil): 0.05 0.2 mg/kg q8 12h PO (dog), 0.05 0.1 mg/kg q12h PO
- Anti-emetics vomiting is often a component of diffuse GI disease and anti-emetics may aid with appetite as well as owner compliance to other treatments. H2 receptor blockers have minimal anti-emetic effect and are used more as antacids. Serotonin antagonists are more potent anti-emetics. Ondansetron (Zofran): 0.5-1 mg/kg PO q12-24h. Dolasetron (Anzemet): 0.5 mg/kg SC, PO q24h. Mirtazapine (Remeron): 15 30 mg PO q24h (dog), 1.875 3.75 mg PO q72h (cat)
- Pancreatic enzyme replacement while we typically use pancreatic enzymes with exocrine pancreatic insufficiency, patients with diffuse gastrointestinal disease may exhibit some degree of malassimilation. Feeding highly digestible diets and pre-digesting food with pancreatic enzymes may improve stool quality by increasing digestion and absorption.

Canine inflammatory bowel disease activity index – a scoring system has been suggested to stage the degree of clinical signs and to better quantify response to therapy.

Parameter	0	1	2	3	Total
Attitude & activity	Normal	Slightly 🗸	Moderately 🗸	Severely $ ellebel{eq:severely}$	
Appetite	Normal	Slightly 🗸	Moderately 🗸	Severely 🗸	
Vomiting	None	1 X / wk	2-3 X / wk	> 3 X / wk	
Stool consistency	Normal	Slightly soft or	Very soft	Watery	
		blood, mucous			
Stool frequency	Normal	2-3 X / d	4 - 5 X / d	> 5 X / d	
Weight loss	None	< 5 %	5 - 10 %	> 10 %	
SUM					

The sum total is used: 0-3 clinically insignificant, 4-5 mild IBD, 6-8 moderate IBD, \geq 9 severe IBD

FOOD COMPONENTS

Hazardous food components encompass dietary components that are present in the food. These may be components that should be present, but are present in an unbalanced manner, or components that should not be present. Nutrient imbalances may occur when there is a problem in the formulation or manufacture of a diet, or if the owner supplements a complete and balanced diet with an incomplete and unbalanced food or supplements. Examples of excesses include hypervitaminosis A (raw liver or cod liver oil) and hypervitaminosis D (recent food recall). Examples of toxicity associated with ingestion of foodstuffs include onion poisoning, which causes a Heinz body hemolytic anemia in cats, and chocolate toxicity, which causes vomiting, diarrhea, and central nervous system disease due to theobromine. Raisins and grapes have been associated with acute renal failure in dogs. Examples of deficiencies include generic foods that may be unbalanced, fat deficiency, and vitamin and trace element deficiencies. Pet foods contain many food additives from antioxidants, to humectants in semi-moist food, to coloring agents. These are approved by the FDA for inclusion in pet foods and are similar to additives used in human foods. Occasionally, food may become contaminated. This may occur if the manufacturer uses contaminated foodstuffs or the food may become contaminated after production. Mycotoxins are a rare problem in pets; however, there have been sporadic reports of mycotoxin-containing foodstuffs being used in the manufacture of dog food resulting in disease and death. Pet foods may become contaminated if mold is allowed to grow. This should not occur in pet foods, but if the food becomes moist or if the fat becomes rancid, it may occur. Occasionally, food may become "spoiled" and bacterial contamination may occur. Such organisms as Salmonella, Campylobacter, and Botulism have been reported. Lastly, ingestion of animal tissues containing residues of toxic substances may result in disease. For example, if a cat eats a mouse that has been killed using a warfarin-like rodenticide, the cat may develop a hemorrhagic disease due to the vitamin-K-dependent coagulation factor inhibition.

MECHANICAL INJURIES.

Food may sometimes contain something that causes mechanical injury to the animal or the animal may ingest such an item. An example is a dog that ingests a bone, which becomes lodged in the esophagus or a cat that ingests a needle with a string attached.

POISONOUS PLANTS AND ANIMALS.

It occurs occasionally $\$ in small animals. For example, ingestion of Easter Lilies results in renal failure in cats.

METALS AND MINERALS.

Lead and zinc toxicity may occur with ingestion.

FOOD ASSOCIATED ILLNESS AND TOXICITY

Recognizing food-associated illness can be difficult as often cases present sporadically with no apparent connection. Recognizing clusters of cases geographically (e.g. regionally) or during the same time period (e.g. animals in same household) is important. Take a good diet history from the owners. Introduction of a new food or a new bag of food, poor palatability or acceptance of the food by the pet(s), and pets eating the same food whether in the same household or different households may provide clues to problems with diet. Keep in mind that animals may present with similar clinical signs and histories but consuming different diets and/or snacks/treats. Discuss cases with your colleagues as they may be having similar experiences that can support your concerns.

Reporting potential adverse reactions:

- Contact the manufacturer they should be willing to listen and take information as well as answer questions as to whether other complaints have occurred
- FDA: <u>http://www.fda.gov</u> specifically
 - FDA: Pet Food site at <u>http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/PetFood/default.htm</u> gives information as to pet food news releases and information for consumers
 - o FDA report a problem: <u>http://www.fda.gov/Safety/ReportaProblem/default.htm</u>
- AVMA: <u>http://www.avma.org</u> specifically, this link for reporting adverse events with drugs, vaccines, and pet food: <u>http://www.avma.org/animal_health/reporting_adverse_events.asp</u>
 - **To report an adverse event associated with pet food (or other animal feed),** please contact your state FDA's Consumer Complaint Coordinator(s). Contact information can be found on the FDA's Web site at <u>http://www.fda.gov/opacom/backgrounders/complain.Html</u>. When reporting, please include as much information as possible, including the specific product name, lot numbers, veterinarian's report and diagnosis, and any other pertinent information.

It is important to gather as much information as possible and to save as much as possible. Document the product name, type of food, manufacturer/distributer information, and date code/best buy code. Keep a copy of the packaging if you can. If the owner has a copy of the purchase receipt, it helps. Retain samples of the food; keep at least 4 cans or pouches of canned or semi-moist food and 1 kg of dry food. Do not send all of the samples for analysis – keep or have the owner keep some. Have the owner document consumption of the food by pet(s) with as much detail as they can recall. Keep good records including signalment, clinical signs, and test results. If a pet dies, perform a necropsy or have a necropsy performed. Make sure to tell the diagnostic lab performing the necropsy of your suspicion of toxicity. Save tissue and fluid samples, if possible. Document communication with the manufacturer and with FDA/AVMA. If other pets may have been exposed, test them. Keep good records and samples of suspect food.

NOTES



TRILOSTANE – GETTING STARTED

Cook AK

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INTRODUCTION

Trilostane (Vetoryl[®]) was licensed for use in the USA for the management of canine hyperadrenocorticism (HAC) in December 2008. The drug itself is not new; it was used in the 1990's for the treatment of adrenal disorders in people and is currently licensed for use in Europe for the management of breast cancer. It was approved for use in Europe for veterinary patients in 2001. It has now supplanted mitotane (o,p'-DDD, Lysodren[®]) as the standard therapy for Cushing's disease in dogs.

Although trilostane is not approved for other uses in dogs, there are several reports describing its efficacy in patients with Alopecia X/Hair Cycle Arrest.¹⁻²

PHARMACOLOGY

Trilostane is a synthetic steroid analogue, and is a competitive inhibitor of 3β -hydroxysteroid dehydrogenase (3β -HSD). This enzyme plays a crucial role in the production of several adrenal cortical hormones. Trilostane therefore has dose-dependent and reversible impact on the production of cortisol. Although the production pathway for aldosterone is also dependent on 3- β HSD, the zona glomerulosa appears to be inherently resistant to the effects of trilostane, and basal serum aldosterone levels are not substantially impacted by trilostane administered at standard doses in most dogs.³ In contrast to mitotane, trilostane is not directly toxic to adrenal cortical tissue. Instead, substantial hyperplasia of the zona fasciculata has been reported in dogs on long-term trilostane.⁴ Grossly nodular hyperplastic changes are often evident on US examination, with measurable increase in the width of the glands.⁵

It is administered orally, and peak levels occur about 2 hours after ingestion. Absorption appears to be somewhat erratic, but administration with food is recommended. The drug undergoes hepatic metabolism, and is cleared from the circulation within 18 hours. The peak effect seems to occur about 4 hours post administration, with measureable diminution of effect by 8-9 hours post dose.⁶ Clearance in some dogs appears to be faster, and there is some controversy about optimal dosing schedule.

The manufacturers state that trilostane should not be used in dogs with renal or hepatic compromise, and avoided in animals intended for breeding. It should be used with caution in anemic patients. Dogs on drugs such as spironolactone and angiotensin converting enzyme-inhibitors may be prone to complications with hyperkalemia. The drug should be used cautiously in this group, with close monitoring of serum electrolytes.

DOSING INFORMATION

Dosing interval: Although the manufacturers recommend once daily dosing, some clinicians feel that twice daily dosing provides better control.^{6,7} I personally find that once daily administration is effective in most patients, and is easier for the majority of pet owners. I only start at twice daily in dogs with diabetes mellitus, as transient hypercortisolemia prior to the next dose may confuse diabetic regulation. Based on studies looking at cortisol production at various intervals after trilostane administration, it seems likely that dogs receiving trilostane once daily will have several hours in which adrenal gland function is not restricted. However, the clinical manifestations of HAC are a reflection of chronic exposure to excessive cortisol, and short periods of higher levels have limited biological effect.

Dosing time: Trilostane should be given in the morning. Follow-up adrenocorticotrophic hormone (ACTH) stimulation tests must be performed at specific times, and evening dosing confuses this issue.

Starting dose: The published starting dose range is 3-6 mg/kg once daily. In my experience, most dogs are acceptably controlled on 2-3 mg/kg daily, and I usually start with this range. If twice a day dosing is planned, this daily dose is simply divided in two.

The drug is presently available in 10, 30, 60 and 120 mg sizes. If a patient is close to the cut off, I will usually round the dose down. It is safer to start at a low dose and slowly increase as necessary. Big dogs in particular seem to be quite sensitive to trilostane, and I rarely start patients at more than 60 mg total daily dose. This personal observation is supported by one study, in which dogs >30 kg required significantly less trilostane on a mg/kg/day basis.⁸

COMPOUNDED TRILOSTANE

Compounded trilostane products are not regulated by the FDA, and serious concerns exist about their pharmacologic properties. In a recent study many products were found to contain substantially different amounts of trilostane than the labeled amount.⁹ In addition, the dissolution characteristics of many of the compounded products were sub-standard, which may impact drug uptake. Liquid compounded products are particularly suspect, due to the inherent solubility issues with this drug.

CLIENT INSTRUCTIONS

Trilostane should be given with food. If the dog is reluctant to eat, do not give trilostane, as this may be a sign of hypocortisolemia. Also, instruct the client very clearly to discontinue trilostane if the dog seems unwell. If the animal vomits or is weak, the client should seek ER assistance. I sometimes send clients home with a small supply of prednisone, to be given at 0.5 mg/kg if the dog is 'blah'. This will effectively address transient hypocortisolemia, and the patient will feel markedly better within 2 hours. The downside to this option is that the prednisone will interfere with adrenal function testing if that is necessary.

ADVERSE EVENTS

Overall, trilostane is easier to use with less side-effects and problems than mitotane. However, adverse events can occur and practitioners should be able to recognize these promptly.

The commonest issue we see is transient hypocortisolemia. This reflects excessive suppression of cortisol production and is manifest by a poor appetite and lethargy. Patients will improve within 2 hours of prednisone administration. Withhold trilostane until appetite is again robust (usually 2 days) and restart with a 50% dose reduction.

A small number of dogs get non-clinical hyperkalemia, due to impaired aldosterone secretion. I have only seen this in dogs on concurrent heart medications (such as ACE-inhibitors). If the serum potassium is more than 1 mmol/L above the reference range, I will decrease the trilostane dose. Bear in mind that dogs with a thrombocytosis (commonly seen in our HAC patients) may have elevated potassium concentrations, due to release of potassium from platelets. This is artefactual, and is not a true hyperkalemia.

Based on its pharmacology, irreversible adrenal compromise is not an expected negative effect. However, several dogs have suffered irreversible adrenal gland necrosis whilst on trilostane, and have become permanently Addisonian. This is a concern, although awareness and prompt recognition make this a manageable side effect. Acute adrenal necrosis was first reported in a dog soon after starting the medication.¹⁰ An adrenal gland was removed surgically and found to be totally necrotic. Other cases have occurred following many stable months of therapy.⁴ Several mechanisms have been suggested, but it appears that severe suppression of the adrenal cortical function may play a key role in the process. Total suppression will result in the massive release of ACTH from the pituitary gland (both from the normal tissue and from the adenoma); rodent studies have suggested that adrenal necrosis is in fact due to excessive ACTH, and not trilostane.¹¹ ACTH excess may have a directly toxic effect on the cortical cells, or the accumulation of huge amounts of a precursor to cortisol may cause cell death.

Patients with adrenal necrosis present with nausea, weakness and anorexia. Initial diagnostics should include measurement of serum electrolytes, and hyperkalemia and hyponatremia should immediately prompt this diagnosis. An ACTH stim test will confirm loss of adrenal cortical function, but treatment for an Addisonian crisis should be initiated pending these results. The prognosis is excellent, and in fact many owners find dealing with a dog with permanent hypoadrenocorticism is simpler and less expensive than managing HAC.

There is one published case report of a dog suffering from permanent hypocortisolemia after three doses of trilostane.¹² This patient maintained adequate aldosterone production, but lost the ability to produce cortisol. This was presumably due to necrosis limited to the zona fasciculata.

COMPARISON TO MITOTANE

Several studies have compared treatment response and long term outcome for dogs with HAC receiving trilostane and mitotane. Overall, the outcome for dogs treated with either agent appears very similar. Median survival times for dogs receiving trilostane range from 2-3 years.^{7,13-15}

SWITCHING FROM MITOTANE

If a patient is well regulated on mitotane, there is little reason to switch. However, if the response to mitotane is disappointing or if the dog does not tolerate the mitotane, moving to trilostane would be appropriate.

Trilostane should be not be introduced until signs of HAC are evident. This may take 2-3 weeks after discontinuing mitotane in a well-controlled dog. Alternatively, an ACTH stim test should be performed; if the post ACTH cortisol is >20 μ g/dl, trilostane can be initiated.

SUMMARY

An understanding of the mechanism of action and pharmacology of trilostane is key to effective therapy. Practitioners should be familiar with current recommendations regarding dosing strategies and educate clients thoroughly about adverse events. Although problems are uncommon, adrenal necrosis is life-threatening and prompt recognition of this event is essential.

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TRILOSTANE – MONITORING AND ADJUSTING

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INTRODUCTION

Monitoring adrenal cortical function in dogs on trilostane is essential, as complications can arise if the dose is excessive or inadequate. Monitoring tools include a clinical assessment (i.e., updated history and physical examination), and biochemical evaluation of adrenal cortical function (i.e., cortisol levels +/- measurement of serum electrolytes).

RECHECK SCHEDULE

The first recheck visit should be scheduled for 10-14 days after staring therapy. Many dogs show some signs of improvement in water intake and urination at this time, although others may take longer to have a clear response. Instruct the client to bring the patient in to the clinic about 3 and ½ hours after trilostane administration, as the adrenocorticotrophic hormone (ACTH) stimulation test should be started 4 hours post dosing.

I usually get the patient back after 4 more weeks on trilostane, and then every 3-6 months. If the dose is changed (either increased or decreased), the patient should be examined within 10-14 days. Any time the dog is unwell, it should be seen as soon as possible.

CLINICAL ASSESSMENT

Decisions regarding trilostane dosing are impacted by the patient's clinical status. Key issues to evaluate are thirst and urination, as persistent severe polyuria and polydipsia indicate inadequate control of cortisol levels, and are often a source of concern and frustration for owners.^{1,2} The physical manifestations of hyperadrenocorticism (HAC) may take months to improve, and owners should be given realistic expectations regarding hair growth and improvement in muscle strength.

Excessive suppression of adrenal function is suggested by poor appetite and lethargy. Clients should be asked specific questions about food intake and energy levels, along with information regarding changes in stool consistency and vomiting.

ASSESSMENT OF ADRENAL FUNCTION

Mineralocorticoid: Although the canine zona glomerulosa appears inherently resistant to trilostane, it is important to check electrolytes to be sure that aldosterone production is adequate. Hyperkalemia strongly suggests suppression of aldosterone production, although dogs with HAC may have a pseudohyperkalemia due to thrombocytosis. Concurrent use of spironolactone +/- angiotensin converting enzyme inhibitors may also contribute to hyperkalemia.

I check serum electrolytes on the first recheck visit, after any increase in trilostane dosage, and if the dog is unwell.

Glucocorticoid: The package insert for the licensed trilostane product (Vetoryl[®]) recommends an ACTH stimulation test on each recheck visit, in order to fully assess adrenal cortical function. As an unpredictable biological effect has been reported with some of the compounded ACTH gels, use of cosyntropin (Cortrosyn[®]) is strongly recommended.³ To reduce costs, a Cortrosyn dose of 5 μ g/kg IV or IM can be used. This has been shown to achieve maximal stimulation of the adrenal glands, with comparable results to the traditional 'whole vial' dose. Once reconstituted, the cosyntropin can be frozen in plastic syringes for up to 6 months, with no loss of potency.

There is a lot of discussion about the 'optimal' post ACTH cortisol concentration for a dog on trilostane. The manufacturers recommend a result between 1.5 and 9 μ g/dl. However, many clinicians

feel that a post-stim cortisol over 5.5 μ g/dl indicates sub-optimal control, and values as low as 3.0 ug/dl have been proposed as the acceptable upper limit for the post ACTH cortisol value.⁴

In my experience, patients with a post-ACTH cortisol between 2 and 7 μ g/dl are usually doing well. The following table describes my personal preferences:

POST-ACTH CORTISOL	TRILOSTANE DOSE ADJUSTMENT
$< 0.7 \ \mu g/dl$	Stop trilostane. Restart until patient shows signs of HAC.
	Restart at 50% of previous dose.
$0.7 - 2.0 \ \mu g/dl$	Decrease dose by 50%
$2.0 - 7 \ \mu g/dl$	Continue present dose
$>7 \ \mu g/dl$	Consider a 25-50% increase in dose if patient shows signs of HAC

If the dog is doing well, both from the owner's perspective and based on my clinical examination, I am reluctant to increase the dose of trilostane, even if the post-ACTH stim cortisol is over 7 μ g/dl. Remember, the dose of ACTH administered during the stim test is physiologically enormous and likely to markedly exceed the amount produced by a pituitary adenoma. If the dog looks good and the client is satisfied, I cannot see the need to increase the trilostane dose just to fit a desired lab work parameter.

If client compliance with ACTH stim test recommendations is poor, a baseline cortisol may be considered. This is a faster and cheaper, and the results are often sufficient to make useful treatment decisions.⁵ In a study looking at 352 ACTH stim test results for dogs on trilostane, correlation was shown between baseline and post-ACTH stim results. If the baseline cortisol is >1.3 μ g/dl, you can be 99% confident that the patient is not overdosed on trilostane, and that a dose decrease is not necessary. If the baseline cortisol is between 1.3 and 2.9 μ g/dl, a dose increase is rarely appropriate.

The baseline cortisol model should be used for patients who appear to have adequate control of their HAC symptoms (based on client reports and your examination) and who are not showing any evidence of hypocortisolemia. This table describes my actions for these dogs:

RESTING CORTISOL	TREATMENT PLAN
< 1.3 ug/dl	Perform an ACTH stim test or decrease dose by 25%
1.3 – 2.9 ug/dl	Continue present dose of trilostane
2.9 - 5.5 ug/dl	+/- Perform an ACTH stim test
> 5.5	Increase the trilostane dose by 25-50 %

MONITORING DOGS WITH HAIR CYCLE ARREST

The impact of trilostane on the levels of cortisol precursor hormones has been investigated in dogs with HAC.⁶ The patterns reported suggest that trilostane may impact activity of 11 β -hydroxylase and 11 β -hydroxysteroid dehydrogenase in addition to 3 β -hydroxysteroid dehydrogenase. Despite positive reports of the clinical effects of trilostane in dog with hair cycle arrest (Alopecia X), there is little information regarding changes in precursor levels in these patients, and the exact mechanism for the positive effect of trilostane is unclear.^{7,8}

As cortisol secretion in dogs with hair cycle arrest appears to be normal, they maybe more vulnerable to hypocortisolemia when on trilostane than dogs with HAC. There is no evidence to suggest that measurement of precursor levels provides any useful guidance in the treatment of these dogs. Instead, cortisol secretion and serum potassium levels should be monitored in the usual manner.

PROBLEM PATIENTS

Persistent signs of HAC: Some patients have persistent evidence of HAC despite on-target ACTH stimulation results. In most cases, this is due to short duration of effect with the trilostane, and is resolved by more frequent administration of the drug.⁹ I leave the daily dose unchanged, but simply divide it and give a portion every 12 hours.

It has been suggested that persistent signs in some dogs may be due to release of biologically active precursor hormones from the adrenal glands. Trilostane does not stop synthesis of many of the precursors, and in some situations, the levels are actually higher. The precursors have some biological effect, and it has been suggested that this is clinically apparent in some individuals. If this appears to be the case, switching to mitotane would be the appropriate option.

If a patient is on compounded trilostane and appears to have a poor response, switch to Vetoryl. The, content and bioavailability of the compounded products is variable and the amount provided may be a fraction of the dose prescribed.¹⁰

The "ADR" patient: On occasion, patients on trilostane manifest clinical signs suggesting hypocortisolemia despite on-target ACTH stim test results. If this occurs at the onset of therapy, the dog may be suffering from "relative" hypocortisolemia. Patients with HAC are physiologically adjusted to high cortisol levels, and may manifest signs such as anorexia or lethargy when those levels are returned to a more appropriate range. In addition, low grade discomfort from old orthopedic or spinal issues may manifest as cortisol levels drop. If "ADR" signs are reported at the onset of therapy, but potassium and cortisol levels are acceptable, I will simply switch the dog to an every other day trilostane plan for 2-3 weeks, and get the dog used to living in a lower cortisol world, before going back to daily therapy.

If a patient becomes inexplicably "ADR" after successful initiation of trilostane, the possibility of a pituitary macroadenoma should be considered.¹¹ Most dogs with pituitary-dependent HAC never show any signs related to the tumor itself, but a small percentage do. It has been suggested that treatment of HAC with adrenal suppressive or adrenolytic agents may in fact hasten the growth of the pituitary tumor, so-called "Nelson's syndrome" from the disorder reported in human patients. Studies of dogs on mitotane have suggested that this does not occur, but similar data has not been reported for dogs on trilostane.¹²

The clinical manifestations related to the pituitary mass mimic those of hypocortisolemia, with intermittent anorexia and lethargy. Some dogs have intermittent visual deficits, but some owners interpret this as reluctance to move or go outside. Ironically, suspension of trilostane can result in a rapid improvement in clinical signs, with improved appetite and mentation. This is most likely due to the impact of endogenous cortisol levels on peri-tumor edema. When the trilostane is discontinued, the edema is mitigated by the cortisol and the dog feels better. In many cases, it can be challenging as a clinician to find any neurological defects in these dogs... full neuro examinations are often normal, with no deficits identified. An MRI with contrast gives the most information about tumor size and compromise to adjacent structures, but a sedated CT scan with contrast is often sufficient to identify a macroadenoma.¹³ Sedation and anesthesia can be a challenge in these patients, due to changes in cerebral perfusion and intracranial pressures. Clients should be warned of these risks.

SUMMARY

Effective therapy of HAC with trilostane requires a thorough understanding of its mechanism of action. Regular patient monitoring is essential in the first few months. Clinicians and owners must be prepared for the time and financial commitment required for necessary follow up.

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