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DERMATOLOGY

With: 

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NEW INSIGHTS ON ATOPIC DERMATITIS: PATHOPHYSIOLOGY AND DIAGNOSTICS, CLINICAL MANAGEMENT

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Learning Objectives:
1. To become familiar with the pathogenesis of atopic dermatitis as it applies to the diagnosis and management of this disease.
2. To understand how to make the diagnosis using history and clinical signs.
3. To understand when and how to use allergy testing
4. To be able to implement a multimodal treatment plan for atopic dogs.
5. To understand how the medications we use for itch and inflammation control work, and to understand the risk/benefit ratio for each.

Pathophysiology and Diagnosis
We have learned quite a bit about allergic skin disease in dogs in the last decade. Understanding the pathogenesis of allergic disease, particularly atopic dermatitis, has allowed us to develop more effective treatments. We see a number of allergic diseases in mammals, but here we will focus on atopic dermatitis in dogs. Atopy is a condition in which mammals develop hypersensitivity reactions to benign environmental stimuli, which include pollens, molds, dusts, danders, mites, and foods. Diseases include those of the upper respiratory tract and ocular mucous membranes, the lower respiratory tract, the gastrointestinal tract, and the skin. We have learned that atopic dermatitis occurs because there is a skin barrier defect, which contributes to disease by permitting absorption of allergens more deeply into the epidermis, where the immune system can access them.

In addition to the skin barrier defects, there is a skewed immune response, promoting the development of IgE and the types of inflammation we see with allergic disease. The immune response is dominated by Type 2 T helper lymphocytes. Every acquired immune response we have is coordinated by T helper cells. T helper 1 cells help mediate the response to intracellular pathogens like viruses. T helper 17 cells fight extracellular pathogens including bacteria and fungi. The T helper 2 cell response was believed to develop in response to large multicellular parasites such as nematodes. By supporting the production of IgE that binds to the parasites, cells such as eosinophils bind the IgE and spew their toxic contents onto the worm to kill it. It is thought that this pathway, in genetically susceptible mammals, has been co-opted for allergies.

Severity of atopic dermatitis is likely dictated by the number of allergic genes a dog inherits, the severity of the skin barrier defect, and the environment in which the dog lives. We now know that dogs absorb most of their allergens through the skin, and this absorption explains why we see the lesions where we do: in sparsely haired areas such as the feet, the perioral and perioral areas, and the ventrum.

In the past, we believed that dogs absorbed their allergens through their oronasal mucosa, and that somehow these were transported in the blood to the skin, where they bound to IgE. This allergen specific IgE was displayed on the surface of mast cells, and the cross-linking of IgE by allergen triggered release of antihistamines and other pro-inflammatory mediators. This belief has led to treatment attempts with multiple antihistamines, most of which work poorly for the moderate to severely atopic dog. Lack of response could be
mediated by improper dosing, but most likely therapeutic failure relates to what we now know is a disease that is much more complex that we previously thought. We now know that most of the clinical signs we see with atopic dermatitis are related to cytokines produced during the Type 2 response. These allergic cytokines result in IgE production, but also the recruitment of eosinophils and other inflammatory cells into the skin. Some of the cytokines involved in the allergic response come directly from the skin cells themselves. And some of these cytokines bind directly to nerves to stimulate itch.

We have learned in the last decade that the itch associated with atopic dermatitis in mammals is due in large part to a Type 2 cytokine called interleukin 31. This cytokine is released during the allergic immune response and it binds directly to nerves to stimulate itch. A second cytokine that can bind to nerves is TSLP which is produced by the keratinocytes themselves during the allergic reaction.

Here is a sequence of events associated with the response to allergens in atopic dogs.

1. The allergenic proteins are absorbed deeply into the epidermis where antigen-presenting cells can capture them.
2. These antigen-presenting cells (dendritic cells/Langerhans cells) process this allergen and carry it to the lymph nodes where they present it to naïve T lymphocytes
3. Naïve T lymphocytes get activated and develop into mature T helper 2 lymphocytes. They produce a series of cytokines (IL-4, IL-5, IL-6, IL-13, IL-31) which instruct B lymphocytes to make IgE and which provoke the allergic response.
4. The T helper 2 lymphocytes and IgE make their way back to the skin. The IgE binds to mast cells as well as the dendritic cells/Langerhans cells and lie in wait for the allergens to come along again.
5. When allergens come along, the IgE on the LC and the mast cells captures them. These cells can then present the allergen to the T helper 2 cells right in the skin and activate the allergic process quickly.
6. Interleukin-31 is released to bind directly to nerves to stimulate itch rapidly. Many of the Type 2 cytokines also stimulate keratinocytes to produce TSLP which also binds to nerves to stimulate itch.
7. Scratching and continued inflammation causes the epidermis to thicken, the number of nerve fibers to increase, and the development of secondary infections. Even more TSLP is produced, and we have a continued amplification cycle of itch and inflammation.
8. Secondary infections promote this abnormal immune response and make the allergic lymphocytes less sensitive to glucocorticoids and normal immune regulatory mechanisms. Ultimately dogs can become allergic to their staphylococci and their Malassezia. Staphylococcal proteins can drive the Th2 response, making allergies worse.
9. Chronic atopic dermatitis appears to be less T helper 2 focused and T helper 1/T helper 17 cytokines also participate in the inflammatory response.

Without intervention, these dogs develop worsening disease and perhaps, like people, they develop autoallergic dermatitis, in which IgE is produced against self antigens released from cells following the trauma of scratching. IgE against keratinocyte-derived self antigens have been described in human atopics, and their presence is associated with a more severe disease manifestation. That this might occur in dogs and cats is suggested by the anecdotal reports of dogs and cats showing skin test reactivity to dog and cat dander respectively. Interestingly the autoreactivity to self antigens is associated with production of IFN gamma and other Th1 cytokines,
explaining the presence of these cytokines in chronic atopic dermatitis. Exposure to self antigens can drive the dermatologic signs even in the absence of exposure to exogenous allergens.

One of the most fascinating findings in atopic dermatitis is the close interplay between the immune system and the nervous system. The skin is considered a neuroimmunoendocrine organ. Skin immune cells and nerves produce neuromediators that function bidirectionally. Immune cells secrete neuromediators that can stimulate nerves to induce vasodilation and plasma exudation. Nerves produce mediators such as substance P, vasoactive intestinal peptide (VIP), and calcitonin gene related peptide (CGRP) affect the function of macrophages, mast cells, and T lymphocytes. Some of the observations in atopic dermatitis include increased density of cutaneous nerve fibers, increased numbers of nerve/mast cell interaction, and a reduced threshold to initiate itch. Furthermore, once stimulated the itch lasts longer than it would in a nonatopic dog!

Diagnosis of atopic dermatitis is made by history and clinical signs, and by ruling out other causes of itch including flea allergy dermatitis and scabies. Atopic dogs tend to demonstrate pruritus early in life and there are several predisposed breeds. In the USA, these includes terriers, the bully breeds (English and French bulldogs, pit bulls and similar dogs, Bostons, Pugs, Maltese, Shih Tzus, setters, and retrievers, and in some locales, German shepherds). Crossbreeds of these dogs can also be affected. The severity of the disease depends on two factors: the genetic background of the dog and the environment in which he/she lives. Dogs that live in warm humid clients tend to be more severely affected, as they are exposed to allergens year round. We now recognize that pure food allergy is not common in dogs. Instead atopic dermatitis can have both environmental and food triggers, making the identification of the triggers for each dog quite tricky. In general, we consider the possibility of food allergy when dogs have nonseasonal itch and when there are gastrointestinal signs. These GI signs can be quite subtle, including increased gut sounds, burping, flatulence, intermittent vomiting, softening of the stool or increased number of stools per day (greater than 3 per day). The only proven way to diagnose food allergy is by diet trial followed by food challenges. The diet we use will be determined by using a good diet history. In general we try to use a novel protein diet and feed for 6 – 8 weeks. If any improvement is noted, we do a food challenge with the old diet to see if itch is exacerbated. If itch comes back within the first week of reintroducing the old diet, then we can do single food challenges to determine what foods the pets can have and what foods they need to avoid. Unfortunately, skin testing or serum testing is not accurate in the diagnosis of food allergy.

By contrast, intradermal testing or serum testing can be helpful in selecting allergens for immunotherapy. In the past, we have said that intradermal testing is superior to serum allergy testing. However, the quality of the serum tests has improved, and at least 4 different studies have shown that immunotherapy based on serum testing can be just as effective as that based on intradermal testing. Analysis of intradermal responses is quite subjective and it is by no means a gold standard. In general, we test for reactivity to pollens, molds, dusts, danders, and mites. In my practice, we find that 30% of dogs and cats are allergic to human dander! Because pets in the USA often sleep in the beds with their owners, identifying allergies to human dander is critical as we can include this in our allergy vaccines. Dogs can be allergic to cats, and cats can be allergic to dogs. We also test for reactivity to Staphylococcus and Malassezia. Many dogs are allergic to these organisms, and we are finding that including these allergens in our immunotherapy can reduce recurrent infections.
Clinical Management
Understanding the pathogenesis of atopic dermatitis in dogs, particularly its great similarity to human disease, has resulted in a change in our approach, and the development of new innovative treatments. Veterinary dermatologists advocate for a multimodal approach based on each dog’s individual presentation.

1. Avoidance. Practically speaking, the allergens most easily avoided are foods and ectoparasites (fleas, other insects). Additional approaches can be taken to minimize allergen exposure to pollens or dust mites. For dogs with pollen allergies, reducing their time outside when pollen counts are high is helpful, as is wiping face, feet, and belly when dogs come back inside. Measures to control house dust mites, for dogs with mite allergies, can reduce itch as well.

2. Immunotherapy. Allergen-specific immunotherapy is the only treatment that actually changes the abnormal immune response. We recommend allergy testing and immunotherapy early in life to help induce tolerance and prevent progression of the disease. In my opinion, immunotherapy works for most dogs, as defined by reduction of itch and inflammation, and reduced need for anti-itch medications. Reduction in staphylococcal and yeast infections also occur. Sublingual immunotherapy has provided us with an alternative to injection therapy, and allergy drops are embraced by many clients. Daily exposure of the immune system to the allergens, as well as improved compliance, may lead to a more rapid and improved response (observed in my practice).

3. Infection control. Many dogs with atopic dermatitis have recurrent staphylococcal and yeast infections, and they can develop allergic reactions to these organisms, which we can determine by intradermal testing and/or serum testing. It can be helpful to include staphylococcal antigen and Malassezia allergen in the immunotherapy (subcutaneous or sublingual) when microbial allergy is found. Bathing is a critical part of infection control and has the added benefit of removing allergens from the surface of the skin. When indicated, systemic antibiotics and antifungal drugs should be used.

4. Skin barrier repair. Optimal nutrition, oral fatty acids, and topical lipid therapy are used to improve the skin barrier. We don’t have hard clinical evidence for any specific products, but preliminary evidence is promising. Reduction in the rate of pyoderma as a result of skin barrier repair is what I have valued, but owners appreciate the improved coat quality and reduction in dry skin and scaling.

5. Itch control. It is critical to control itch in atopic patients, so that owners can tolerate the time it takes for immunotherapy to work well. The most effective agents include glucocorticoids, cyclosporine, and oclacitinib.

Glucocorticoids have been used for years to control itch. Glucocorticoids work by binding to intracellular glucocorticoid receptors; these receptors bind to DNA to induce or repress several genes. These glucocorticoid receptors are expressed in many tissues, explaining the many potential side effects we can see. When we can use low doses of glucocorticoids every other day, we can manage many atopics for years with minimal side effects. Many dogs though become refractory to lower doses and as each year passes, need to increase the doses to those which cause serious side effects. A useful tool is the “safe steroid” equation popularized by Dr. Candace Sousa. We take the body weight in kilograms and multiply it by 30. That gives us the mg of prednisone or prednisolone a dog could take in one year with minimal side effects. For a 10 kg dog, you would give 300 mg PER YEAR. That is about 2 mg every other day. When using Temaril-P® (trimeprazine/prednisolone, Zoetis), the dog would take 1 tablet every other day. If the trends suggest that the dog will require more than this to control itch, glucocorticoids are much less desirable for long term management.
When cyclosporine (Atopica®, Elanco) became available, we were able to treat the itch of dog with diabetes or Cushings syndrome, or other medical conditions preventing the use of glucocorticoids. Cyclosporine binds to an intracellular molecule called cyclophilin; this complex binds to an intracellular phosphatase called calcineurin, inhibiting its function to activate the transcription factor called NFAT. This inhibition prevents the activation and proliferation of T lymphocytes and it also represses the production of cytokines such as IL-2; there are effects on other cells as well. We use the drug at 5-7 mg/kg daily for 4-6 weeks, then slowly taper to the dose that controls the disease. In some areas, dogs may need to take cyclosporine daily and for larger dogs it can be quite expensive. A recent literature review confirms the long term safety and efficacy of Atopica® for the treatment of canine atopic dermatitis. It does not appear to be effective for flea allergy dermatitis or food allergy. The most common side effects seen are gastrointestinal.

One of the newest innovations in the treatment of atopic dermatitis is the JAK1 inhibitor oclacitinib (Apoquel®, Zoetis). Ten years of development and testing has led to a novel targeted treatment for allergic itch control, which many clients call amazing. For most dogs, dramatic reduction in itch and inflammation is seen within a matter of hours, with few side effects. When used according to directions, this drug has provided substantial itch control for chronic atopic dogs for over 2-4 years, with minimal side effects. JAK1/3 pathways are utilized by the cytokines in the allergic pathways, so the treatment is quite targeted, and spares the cytokines that mediate innate immunity and bone marrow function (JAK2). This is the first JAK inhibitor in veterinary medicine and is the most targeted JAK1/3 inhibitor, as the current JAK inhibitors used in human clinical medicine are considered pan-JAK inhibitors. Oclacitinib can be used for acute allergic eruptions as well, and is very well tolerated. Its discovery and development is a direct result of our new understanding about the pathogenesis of atopic dermatitis. It appears to be successful in managing the itch associated with flea allergy, food allergy, and contact allergy as well as atopic dermatitis.

Very recently, Zoetis received a conditional license for the use of a caninized monoclonal antibody directed against canine IL-31 (Canine Atopic Dermatitis Immunotherapeutic). This monoclonal antibody binds IL-31 to prevent its binding to its receptor. The label dose is 2 mg/kg given subcutaneously every 4 weeks. Studies have shown that this monoclonal antibody reduces itch in atopic dogs within 24 hrs. The duration of relief in some dogs is greater than 4 weeks. It was found efficacious in 80% of dogs with atopic dermatitis. This approach is biologic rather than than pharmacologic, and the safety profile has been excellent.

Selected References:
Bieber T. Atopic dermatitis 2.0: From the clinical phenotype to the molecular taxonomy and stratified medicine. Allergy 2012, Dec;67(12):1475-82.


MANAGING PYODERMA IN THE 21ST CENTURY

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Learning Objectives:

1. To understand why dogs get pyoderma.
2. To be able to identify the common underlying causes for pyoderma.
3. To be familiar with the most common bacterial cause of canine pyoderma.
4. To understand the difference between methicillin resistant Staphylococcus pseudintermedius (MRSP), the canine pathogen, and methicillin resistant Staphylococcus aureus (MRSA), and why it matters.
5. To recognize the clues that a MRSP is present, and how to culture.
6. To understand the antibiotic choices when MRS is present, and the vital importance of topical therapy in managing canine pyoderma in general, as well as in those cases associated with MRS.

Pyoderma is a common skin disorder in small animal practice. Yet it remains a frustrating disorder as Staphylococcus tends to be an opportunist which takes advantage of compromised skin. Sorting out the diseases which predispose to pyoderma is a critical feature of infection management, yet many pyodermas become recurrent. We often consider underlying diseases but we may not consider features such as owner and patient compliance, suboptimal dosing, incorrect choice of antibiotic, and an overall reduction in the use of topical therapy. The age of methicillin resistance is now with us in veterinary medicine and we are struggling with how best to deal with this phenomenon which has plagued physicians for some time. The increase in prevalence of multi-drug resistant bacteria is sadly coupled with decreased antibiotic drug discovery and development, so veterinarians and physicians are coming back to old antibiotics for treatment of resistant bacteria as well as nonantibiotic topical therapy, which is particularly suited for dogs with pyoderma. It is important to realize that the best protection against spread of MRS in both humans and dogs is hygiene. Handwashing, the use of alcohol-based hand cleaners, and environmental disinfection do more to reduce the spread of infection than antibiotics can. The next best protection is to use antibiotics wisely. Modern recommendations include using the highest safe dose the pet can tolerate for only the amount of time it takes to clear the infection. The idea is to kill off susceptible bacteria so rapidly that the host’s defenses can take over; in this way we prevent selection of resistant strains of bacteria.

Why do dogs get pyoderma?

Of all the species with which we work, the dog seems uniquely predisposed to bacterial skin infections. Basic structural features of their skin make dogs more susceptible to skin infections. Unlike human haired skin, dog hair follicles lack the protective lipid plug that blocks the hair follicle opening; in addition dogs have a thin and relatively disordered stratum corneum with less intercellular lipid. In general, the pH of dog skin is believed to be more alkaline that that of human skin and other domestic animals, with acid pH’s considered to be more antimicrobial. Dogs with underlying skin disorders, such as atopic dermatitis and other allergic skin conditions, disorders of keratinization, endocrinopathies, and parasitic diseases, are more likely to develop staphylococcal skin infections. We know that the skin barrier, represented by the stratum corneum, is one of the first physical and chemical defenses against microbial infection. This barrier is known to be defective in human patients with atopic dermatitis and disorders of keratinization; we now know that this barrier is defective in dogs with atopic dermatitis as well. In addition, preliminary evidence suggests that dogs with atopic dermatitis may have decreased levels of defensins, cationic antimicrobial proteins that defend
against bacterial infections as part of the innate immune system. In spite of this preliminary evidence, we are a long way from truly understanding why staphylococcal infections are so common in dogs.

**What bacteria cause pyoderma in dogs?** The major canine skin pathogen is *S. pseudintermedius*; however, *S. schleiferi*, *S. aureus*, and *Pseudomonas aeruginosa* also can be identified from canine patients with pyoderma. *S. pseudintermedius* binds preferentially to canine skin cells compared to human or feline skin cells, and this binding is enhanced when the corneocytes are derived from atopic dogs. While not considered as virulent as the human pathogen *S. aureus*, *S. pseudintermedius* shares many of its virulent characteristics, including enzyme and toxin production, ability to adhere to matrix adhesive proteins, and ability to form biofilms. Each of these features contributes to the ability of the bacterium to colonize and invade the skin. *S. schleiferi* was first identified from human clinical specimens in 1988. It has now been identified as the cause of pyoderma and otitis externa in dogs as well. *S. aureus*, the human pathogen, has been identified in a low percentage of dogs. Last, while not common, *Pseudomonas aeruginosa* can also be identified from the skin of dogs, particularly in lip fold pyodermas and post-grooming folliculitis.

**How do we diagnose pyoderma?** The clinical appearance of the lesions supports the diagnosis but we nearly always perform cytologies, because staphylococcal infections often coexist with *Malassezia* infections, and both need to be treated in order to resolve the skin problem. Clear acetate tape can be pressed on the lesions The tape is easily stained with the rapid modified Wright’s Giemsa stain Diffquick/Diffquik. The critical feature when using this staining system is to skip the first part, the light blue methanol fix, which will melt the adhesive off the slide or make the tape cloudy and more difficult to evaluate. Once stained, the tape will serve as its own coverslip. It is placed on the slide, immersion oil applied, then the slide examined for microbes, keratinocytes, and white blood cells. Culture and sensitivity is recommended for all generalized deep pyodermas and when treatment with two different classes of antibiotic fail to resolve the problem. Methicillin resistance in canine infections is increasing and the sensitivity results are required to pick the correct antibiotic, as we don’t have validated methods for empirically picking antibiotics for methicillin resistant staphylococcal infections in dogs. Moreover, identifying the particular *Staphylococcus* species involved is important so that we can determine whether the dog is infected with methicillin resistant *Staph aureus* and may be a source of contagion to humans. While there is some risk when dogs have MRSA, the important concept to remember is that these dogs most likely got the infection from a human. MRSP is much less likely to cause human infections, unless a person is very young, very old, or immunocompromised. Even then, the risk is relatively low (see http://www.wormsandgermsblog.com/promo/services/)

**How do we treat pyoderma in dogs?** Most dermatologists believe that the most appropriate first choice antibiotic for canine pyoderma is a cephalosporin or other beta-lactam. The International Society for Companion Animal Infections Diseases (ISCAID) recently published guidelines for the treatment of superficial pyoderma (see reference below). Recommended first tier antibiotics include clindamycin or lincomycin, amoxicillin-clavulanate, cephalixin, or cefadroxil. Potentiated sulfas, cefpodoxime, and cefovecin were considered either first tier or second tier. My personal preference is to use cefovecin and cefpodoxime as my first tier antibiotics. My rationale is that there is considerable geographic variation in the efficacy of antibiotics, and in my geographic area, cephalixin or amoxicillin-clavulanate used twice daily fails at least 50% of the time, and clindamycin is often associated with the development of resistance during treatment. Most dermatologists will recommend against choosing a fluoroquinolone as a first choice for pyoderma management. There are several reasons for
this. First, enrofloxacin in particular has been used extensively in many dogs, often at doses that are suboptimal for Staphylococcus spp. Second, the fluoroquinolones do not seem to be as effective in vivo against S. pseudintermedius as predicted by in vitro sensitivities. This is particularly true for older fluoroquinolones such as ciprofloxacin and enrofloxacin. Third, there is concern that fluoroquinolones may actually increase the risk of selecting for resistance. In humans, the relative risk for developing infections with MRSA were highest for those patients treated with fluoroquinolones compared to other antibiotics. Furthermore, the use of older fluoroquinolones, in particular ciprofloxacin, was highly associated with selection for resistance.

<table>
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<tr>
<th>Table of Antibiotic Doses for Canine Pyoderma</th>
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<tr>
<td>Cefovecin (Convenia)</td>
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<td>Cefpodoxime (Simplicef)</td>
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<td>Cephalexin</td>
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<td>Lincomycin (Lincocin)</td>
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<td>Clindamycin</td>
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<td>Amoxicillin-clavulanate (Clavamox)</td>
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<td>Ormetoprim-sulfadimethoxine (Primor)</td>
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<td>TMP-sulfa</td>
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<td>Doxycycline (if sensitive)</td>
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<td>Minocycline (if sensitive)</td>
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<td>Marbofloxacin (Zeniquin)</td>
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<tr>
<td>Enrofloxacin (Baytril)</td>
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<tr>
<td>Ciprofloxacin (not recommended)</td>
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<td>Chloramphenicol</td>
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<td>Amikacin</td>
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<td>Rifampin</td>
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*** Ciprofloxacin, while inexpensive, is a second generation fluoroquinolone with less activity against gram + bacteria than we would like. It has been shown in 2 different studies to be very inconsistent in absorption.

**** Keep dose at a max of 10 mg/kg/day to reduce risk of hepatic damage, including necrosis and death.

What is methicillin resistance and how do we recognize it? Methicillin resistance in Staph is associated with acquisition of a gene mecA that incorporates into the bacterial genome and is subsequently passed on to all daughter cells. Mec A, codes for a mutated form of penicillin binding protein on the surface of the bacteria. The mutant protein can’t bind any beta-lactam antibiotic and thus all penicillins and cephalosporins will be ineffective. The genetic element on which the mec A gene resides can also carry other antibiotic resistance genes and thus some Staph pseudintermedius will be resistant to all antibiotics tested. This genetic element will be retained within the Staph as long as antibiotic pressure is present, but in some cases it can slow bacterial growth. If antibiotic pressure is removed, then the bacteria have the capability of excising the incorporated genetic element and becoming sensitive again. For this reason, it may make the most sense to avoid systemic antibiotic therapy for dogs with superficial pyoderma caused by MRS and focus on aggressive topical therapy. To diagnose methicillin resistance, we must do culture and sensitivity. It is no longer acceptable for your lab to report out coagulase positive Staph spp. You should demand that the species of the Staph be determined,
particularly when the infection is reported as methicillin resistant. Also, it is very important to be precise in our terminology. A methicillin resistant Staph. pseudintermedius is not “MRSA” but “MRSP.” The term “MRSA” refers specifically to methicillin resistant Staph aureus, the human pathogen.

**How do we treat methicillin resistant pyoderma in dogs?** Systemic antibiotic therapy for dogs with MRS cannot be picked empirically. Culture and sensitivity is required to know what antibiotic will likely be effective. Given that systemic antibiotic therapy drives the retention of the resistance factors, maybe we need to shift the way we think about superficial pyoderma and use topical antiseptic therapy instead. We hypothesize that topical therapy may give the bacteria time and opportunity to eject the resistance genes and become susceptible again. To test the hypothesis that dogs with methicillin resistant superficial pyodermas could be cleared with topical therapy alone, we recommended daily topical therapy for 10 dogs with methicillin resistant Staph pseudintermedius (MRSP). All dogs were cleared of clinically observable infection within 30 days, and most were substantially improved within 2 weeks.

Clearly not all dogs with MRS will respond to topical therapy, particularly if the infection is a deep pyoderma. For those dogs, systemic antibiotic therapy will be required and culture and sensitivity will be mandatory. If the organism is sensitive, potentiated sulfas offer a great option for dogs with MRS. While side effects are possible, most dogs tolerate these drugs quite well. If reported as sensitive, clindamycin can also be used. A resistance factor termed the clindamycin-inducible resistance factor can be found in Staph spp; one indicator that this gene might be present is reported resistance to erythromycin but sensitivity to clindamycin. Treatment with clindamycin will rapidly induce the resistance factor, and antibiotic therapy will fail. It is only recommended, therefore, to use clindamycin if the bacteria are reported sensitive to all macrolides. Although we have advocated against the use of tetracyclines for most Staph pseudintermedius, MRSP may revert to sensitive. In those cases, doxycycline or minocycline may be helpful. My experience has been that long courses are required, as these antibiotics are bacteriostatic. The majority of MRSP are sensitive to rifampin and amikacin. Amikacin is well tolerated by most dogs but must be given by injection and does have the risk of renal toxicity. Frequent monitoring of the urine for casts and repeated bloodwork (BUN, creatinine) can make this an expensive option. Rifampin can be used effectively but it has the potential to cause hepatotoxicity. Monitoring liver enzymes every 1-2 weeks is recommended.

**Why is topical therapy so important in the treatment of pyoderma?** Topical therapy should be part of the regimen for all dogs with pyoderma. Bathing removes scale, grease, and crust, reduces odor, and makes the dog feel and look better. Furthermore, topical therapy will accelerate the rate to cure, and hopefully decrease the length of time oral antibiotic therapy will be required. When used regularly, topical therapy may help reduce the frequency of relapse for dogs with recurrent pyodermas. Several shampoos are available for use, but current evidence suggest that shampoos containing 2-4% chlorhexidine are most effective. If bathing is done as monotherapy for resistant bacterial infections, then it is best done daily with a chlorhexidine –based shampoo, in my opinion. For those clients who cannot bathe every day, sprays and mousses are available. Economical but very effective options can be used topically daily for dogs that cannot be bathed. One of the most effective topical agents for methicillin resistant staphylococci is sodium hypochlorite, the active ingredient in bleach. Even very diluted concentrations of bleach can be very effective. Pediatric human patients are treated with compressed soaked in household bleach 5-6% diluted to ¼ cup per 10 gallons of water. This equates to 60 mls per 10 gallons or 6 mls per gallon. Solutions can be mixed up and put in a sprayer bottle to apply directed to the
affected sites. For facial lesions, ocular lubricant can be applied to the eyes, and compresses soaked in the solution applied. There are two veterinary shampoos utilizing sodium hypochlorite and salicylic acid: Command™, Vetrimax, and Canine Skin Solutions Recovery Shampoo, CSS™Canine Skin Solutions. These shampoos are well received by clients and appear effective clinically; publications are pending.

Bacterial pyoderma in dogs is considered a secondary disease and when it recurs, we try to determine whether underlying causes exist. The major considerations for recurrent pyoderma include parasitic diseases such as demodicosis or scabies, allergic skin disease, endocrinopathies such as hypothyroidism, hyperadrenocorticism or diabetes mellitus, and disorders of keratinization.

REFERENCES AND RESOURCES:
An excellent resource for information about methicillin resistant staphylococcal infection is Worms and Germs Blog. http://www.wormsandgermsblog.com/ On this site you can find information sheets for clients that help explain the difference between MRSA and MRSP.

Hillier A†, Lloyd DH, Weese JS, Blondeau JM, Boothe D, Breitschwerdt E, Guardabassi L, Papich MG, Rankin S, Turnidge JD, Sykes JE.
THE SKIN IS ON THE OUTSIDE: TOPICAL THERAPY IN SKIN BARRIER REPAIR

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Learning Objectives:
1. To be able to define the skin barrier and its function when normal.
2. To understand the impact of an impaired skin barrier.
3. To be familiar with the products available for skin barrier repair and how they are used.

Topical therapy is enjoying a much-needed renaissance in veterinary dermatology, and it is about time! We have gotten out of the habit of using topical therapy in dogs and cats in the last couple of decades, yet it remains a very helpful treatment modality, particularly in this day of resistant bacterial infections. One of the newer approaches is the application of lipids directly to the skin, to facilitate repair of the skin as well as improve coat and skin quality. We lack large numbers of publications supporting efficacy at this time, but they are coming, and anecdotal experience suggests that these products can be quite helpful.

The driving force for the use of topical lipids is based on the observations that human patients with atopic dermatitis have skin barrier defects. While the defects are quite complicated and consist of alterations in both structural proteins and lipids, decreased levels of ceramide have been observed and treatment with topical ceramide and other lipids have been quite effective. Topically applied lipids are believed to help the skin repair itself.

There are two major hypotheses for atopic dermatitis. The traditional “inside-out” view, as proposed by allergists/immunologists, is that all of the abnormalities seen with atopic dermatitis could be attributed to the immunological abnormalities associated with the atopic state. Traditionally, these abnormalities have been reflected by increased allergen-specific IgE, but involve many other dysregulated immune responses. By contrast, dermatologists have proposed that the barrier defects observed in human atopic patients play an active role in the disease, and are not simply the result of an abnormal immune response, the “outside-in” hypothesis. Clearly both are involved, but the lipid defects seen in atopics provide a novel approach to treatment. In fact, ceramide applied topically to pediatric patients was equally effective after 28 days of application when compared to topical fluticasone (1).

Recent publications suggest that the lipid composition of the stratum corneum in dogs is quite similar to that in humans, and that ceramide levels are decreased in atopic dogs as they are in atopic humans (2-4). Moreover, the application of the prototype for Allerderm Spot-on® (Virbac, containing ceramide and fatty acids) was shown to restore the level of lipids in the stratum corneum of atopic dogs to that of normal dogs (5). Prior to the use of topical ceramide, many veterinary dermatologists were using the lipid phytosphingosine, a ceramide precursor. Phytosphingosine is the key ingredient in the DOUXO® line of products by Sogeval (CEVA). Phytosphingosine, in addition to having antimicrobial and anti-inflammatory effects, has recently been shown to reduce histamine-induced scratching in mice and also inhibited the allergic cytokines that follow histamine release (6).

Currently there are four product lines containing topical lipids, but more are coming: Allerderm Spot-on® (Virbac) containing a complex of ceramides and fatty acids, Dechra’s shampoos which contain ceramide
complex, the DOUXO® line (Sogeval) of shampoos, sprays, gels, ear washes, and spot-on, containing phytosphingosine, as well as other active ingredients, and the Dermoscent® line of spot-on, emollient balm, mousse, and sprays. This last is made from a mix of essential oils derived from grains and herbs which supply high levels of fatty acids to the skin.

**ALLERDERM SPOT-ON®**

We have had the chance to use this topical product in over 60 dogs with atopic dermatitis, including those with recurrent pyoderma. We expected to see improved coat quality and skin quality, as many atopic dogs have noticeably dry skin. What we also observed, however, was a reduction in the rate of recurrent pyodermas and in mild atopic dogs, reduction of itch. It is likely that any dog with dry and scaly skin would benefit from this type of treatment. The product comes in 2 sizes, 2 mls for dogs less than 10 kg and 4 mls for dogs over 10 kg. It is a milky nongreasy odor free liquid that is applied to multiple spots on the body and it can be touched safely by the owner. Initially I have used this product twice weekly for 3 weeks, then weekly for 3 weeks, then every 2-3 weeks. Some of our clients have found that the direct application to early “hot spots” and foci of pyoderma will rapidly resolve the condition. I have found that this topical medication, when combined with Staphage Lysate, will help prevent recurrence of pyoderma in some non-atopic dogs as well. A recent publication provides preliminary evidence for efficacy in atopic dermatitis (8), but more work needs to be done. Unfortunately this product is no longer available in the United States.

**DOUXO®**

The Douxo® line of shampoos, sprays, ear flush, gels, and spot-on are used enthusiastically by many veterinary dermatologists for a variety of skin diseases. These products are extremely elegant and easy to use. Sogeval/CEVA has provided guidelines for use which in general promote the idea that twice weekly bathing initially is helpful, followed by the use of the sprays as replacement for the baths. The Seborrhea shampoo is truly remarkable for its ability to treat both dry and oily forms of seborrhea. Many seborrheic dogs which usually need baths 2-3 X per week with traditional antiseborrheic shampoos can be reduced to once every week or two. This shampoo and spray have been very useful in the management of sebaceous adenitis, reducing the labor associated with the topical therapy used for this disease. We have found great use for the DOUXO® chlorhexidine shampoo and spray in the management of methicillin resistant staphylococcal infections. We have recommended bathing 2-3X per week, with daily applications of the spray in between baths. A recent publication showed that bacterial counts on the skin surface were reduced with this shampoo, but were not significantly different from the shampoo vehicle; it was a very small study though (9). Thus it may be that is the physical action of bathing that contributes a great deal to the efficacy of bathing. The DOUXO® Micellar ear cleaner is excellent, and really does a good job of emulsifying waxy exudates. This product is often tolerated by dogs that cannot tolerate other ear cleaners. The DOUXO® chlorhexidine PS pads (which also contain a great antiyeast medication called climbazole) have been a welcome product for the cleaning of skin folds and the local treatment of yeast dermatitis in the feet. We have found the DOUXO Calm® Gel to be particularly good at arresting the development of hot spots, giving the client an option at home before the lesions become very inflammatory. The Calm® formulation of the DOUXO® mousse has been shown to help reduce skin pH and repair the skin barrier in a canine model of skin barrier disruption.(10) The Spot-on has many uses as well. It can be spotted onto multiple places on the body for atopic dogs, but it is very helpful in the management of scaly cats,
as a local treatment for chin acne in both dogs and cats, and as a treatment for hyperkeratotic noses and calluses. In addition, it has been used in ears twice weekly to help reduce cerumen buildup in ceruminous otitis externa. It is also helpful as a topical therapy for the hyperkeratotic feet seen in older Amazon parrots. This spot-on is also non-greasy and odorless, and safe for owners to touch. More information can be obtained from the Sogeval website, which is currently being enhanced. (http://www.sogevalus.com/derm_phyto.html)

DERMOSCENT®

This product line has been used in Europe for the last few years and has recently been introduced into the US. Two publications to date has demonstrated some efficacy in the treatment of atopic dogs (7, 11); however, there are a number of case reports and poster presentations made at several meetings. We have our most experience with the Essential 6® topical lipid spot-on and the Bio-Balm® emollient. We have also used the Mousse to less extent. These products have a slightly oily feel and a pleasant herbal odor. They are very popular with our client who like “natural” products. They are recommended to be applied once weekly for 2 months then every 2-4 weeks or as needed. We have observed great improvement in coat quality and skin quality in several dogs with scaling disorders, and a reduction in the rate of pyoderma recurrence in atopic dogs. In particular, many of my colleagues enjoy using this product in the treatment of sebaceous adenitis. I have recently started using it in dogs with sebaceous adenitis as well, and these patients look much less scaly and crusted, with reduced frequency of bathing. There is a topical spot-on product made for horses as well; there are anecdotal reports that it has been useful in the treatment of horses with Culicoides hypersensitivity. We are using the BioBalm® for hyperkeratotic noses and calluses, and as treatment for rough dry patches of skin found on other parts of the body. The mousse seems particularly well suited to cats; we have also used it as a gentle cleaning and moisturizing agent for dogs with pemphigus foliaceus. It is the best deodorizer we know following expression of anal sacs! Further information about these products can be found on the Dermoscent® website. These products are readily available to the client on line, so stocking them in the clinic may not be required. (http://www.dermoscent.com/?lpg=EN)

CERAMIDE Complex is now added to many of the Dechra lines of shampoos as well. This complex contains ceramides 1, 3, and 6, along with cholesterol and fatty acids. In addition, Canine Skin Solutions® Recovery shampoo (http://www.healthyskin4dogs.com/ingredients/) and VetBioTek’s shampoos and products contain ceramides as well as microsilver (http://vetbiotek.com/vetbiotek-products/). We believe that using these types of shampoos over time will help restore the skin barrier.

SUMMARY

We are still in the early days of discovering how best to use these products. Our sense is that there may be some differences among the three types of products with regard to specific applications and specific diseases. We anxiously await further studies and clinical trials.

REFERENCES


Learning Objectives:
1. To appreciate the complex nature of otitis externa in dogs, with regard to predisposing, primary, and perpetuating causes.
2. To develop a standard approach to the diagnosis of otitis externa based on clinical appearance and cytology results.
3. To appreciate when a culture and sensitivity will provide value for treatment.
4. To be able to develop an effective maintenance treatment plan for dogs to prevent relapse.
5. To develop an effective protocol for the treatment of severe and chronic Pseudomonas infections.

Otitis externa is a common problem in dogs, and its treatment can become frustrating for owners, dogs, and veterinarians! Acute uncomplicated infectious otitis can often be treated easily and quickly, but chronic or recurrent otitis externa can be difficult. Repeated bouts of inflammation and infection can cause secondary changes in the ear canal that ultimately lead to end stage ear, requiring a total ear canal ablation. Treating ear infections effectively, and determining why they recur is critical to success. Cytology is one of the most useful tools we have. Culture and sensitivity has become more important as we continue to deal with resistant staphylococcal and pseudomonal infections. Cleaning the ears is very critical to break up the biofilm that protects the bacterial colonies from the topical or systemic antibiotics. Once infections are cleared, maintenance ear flushes can be used to prevent recurrence as we work to determining the underlying causes.

Etiologic and Pathophysiologic Points:
1. Dogs, by the nature of the L-shape of their ear canals, are prone to ear infections.
2. Underlying causes of otitis include predisposing factors (e.g. conformation), primary factors (e.g. allergies, foreign bodies), and perpetuating factors (bacterial, yeast, fungal infections).
3. Any swelling or inflammation in the ear causes closure, retention of moisture and secretions, and increase in cerumen gland secretions. Infection subsequently results.
4. Secondary hyperplastic and inflammatory changes complicate our treatment plan and must be addressed.
5. Major bacterial causes of otitis include Staphylococci, Pseudomonas, Streptococcus. We also see Enterococcus, other gram negative infections, and Corynebacteria. Malassezia is also a major cause of otitis; some dogs appear to develop an allergic response to the yeast, creating great pruritus. Occasionally fungi such as Aspergillus spp can cause otitis externa.
6. Staphylococci and Pseudomonas produce biofilm, which must be disrupted before any topical therapy or systemic antibiotics can be effective.
7. Dogs with chronic ear infections, particularly those caused by Pseudomonas often develop otitis media, which may not be associated with vestibular signs.

Clinical Diagnostic Points:
1. Thorough otic exam and ear canal palpation.
a. Hand-held otoscope.
b. Video-otoscopy
2. Cytology to select appropriate treatment empirically.
3. Culture and sensitivity when empirical choices fail.
4. When indicated, advanced imaging (CT, MRI) is required to check for the presence of middle ear infection or masses, as well as bony infection.
5. Determine underlying cause to prevent or reduce recurrent infections.

Therapeutic Points:
1. The use of steroids (topical, systemic) to reduce inflammation and pain, and to prevent secondary changes
2. Cleaning the ear to remove biofilm and exudate (sedation or anesthesia if indicated).
3. Topical therapy based on cytologic findings. Be sure to use enough medication to completely coat the ear canal.
4. Systemic antimicrobial therapy may be required for some patients (otitis media, erosive/ulcerative otitis externa).
5. Correct the underlying cause if you can, manage it if you can’t.

Prognostic Points:
1. Effective use of steroids will help prevent secondary changes that lead to end stage ear.
2. Topical and/or systemic therapy should be based on cytology, and when indicated, culture and sensitivity; duration should be long enough to completely resolve infection.
3. Monitoring by cytology every 2-3 weeks will determine when treatment can be stopped. If stopped too soon, relapse results.
4. Regular ear care is required to prevent recurrence.
5. Calcification and/or the presence of secondary proliferative changes in the ear canal are indications for total ear canal ablation

Otitis externa is a common and frustrating clinical problem in dogs. The L-shaped ear canal allows for accumulation of exudation deep in the ear. Anything that permits inflammation in the ear canal will cause swelling, and this swelling further promotes exudate occlusion. Breeds such as Pugs, English bulldogs, and Sharpeis have a twist in their ear canals; any inflammation can swell the ear canal shut. For these reasons, we emphasize not only treating the infection but trying to determine why they are occurring.

Most dermatologists and otologists separate the causes of otitis into the 3 P’s: predisposing factors, primary factors, and perpetuating factors. Predisposing factors are those that make an individual dog more susceptible to developing ear infections. These include conformation as we alluded to above, as well as activities such as swimming and environmental conditions such as humidity and high temperature. Other predisposing factors can include trauma to the ear canal, such as over aggressive cleaning or hair plucking. Primary factors are those causes that directly initiate inflammation in the ear canals. These can include parasites such as ear mites or ticks, foreign bodies such as grass awns, allergies such as food allergy, atopic dermatitis and perhaps flea allergy, keratinization disorders such as those seen in Cocker spaniels, tumors or polyps within the ear, and sometimes immunologic diseases such as pemphigus foliaceus. Perpetuating factors are what we most often treat:
infections with bacteria, yeast, or fungi. But chronic changes in the ear will also perpetuate ongoing inflammation and make infections particularly difficult to cure.

The general tools that I like to use when treating otitis include a good history, a thorough otic and dermatologic exam, and the use of cytology to determine what type of infection is present. Historical facts of importance will include whether the otitis is acute, recurrent, or chronic, whether the signs have been seasonal, whether other dermatologic disease has been observed, and whether vestibular signs have been seen. A thorough otoscopic exam is really important and this may require sedation. If the ear is too painful or swollen shut, it is best to put the dog on a course of glucocorticoids and recheck the ear in 7-10 days. Sedation may still be needed, but at least the dog will be feeling much better and good cytologies will be easier to obtain. Cleaning the ear is a critical part of the treatment plan, and I really believe the initial cleaning is best done in the veterinary office. Cleaning is essential because the bacteria causing these infections can often make biofilm, which protects the bacteria from any topical antibiotics we would like to use. I like to use Cerumene, a squalene-based cleaner, which seems to be very good at emulsifying thick waxy or mucous-like exudates. The use of the Auriflush (Intervet/Schering-Plough) can really enhance removal of exudates so that you can start with a clean ear. Prior to dispensing otic medications, it is essential to determine whether the owners will be able to treat the ears at home. If not, it is better to consider the use of BNT ointment or preferably ear wicks. BNT (Baytril, Nizoral, triamcinolone) is made by BCP Compounding Pharmacy in Houston, TX. This ointment is a repositol which is very good for yeast infections and mild bacterial infections, but it is imperative that the ear drum is intact. Ear wicks are great as they minimize owner contact with the ear. The wicks are placed into a cleaned and dried ear, and then wetted with the solution of choice. They can be left in for 1-2 weeks, with wetting every 3-4 days. We obtain our ear wicks from Jorgenson Laboratories, Loveland CO (www.JorVet.com).

No matter the cause of otitis, we have learned that nearly all dogs with inflammatory ear disease will benefit from glucocorticoid therapy. Glucocorticoids help to reduce pain and swelling, opening the ear canal so that we can clean and medicate it. Furthermore, by drying the ear, glucocorticoids actually can reduce bacterial counts and in some cases, seems to disrupt the formation of biofilm. Glucocorticoids, used early in the course of disease, can help prevent the development of chronic changes that perpetuate the disease.

There will be differences in the approach to acute vs chronic otitis, but cytology is always essential in order to pick the correct medication. Swabs are taken and rolled onto glass slides. Otic cytologies are heat-fixed to help prevent the loss of diagnostic material for yeast. Our practice uses Diff-Quick stain for ear cytologies, which is helpful to diagnose yeast, cocci, and rods. Gram staining is an additional tool that will help differentiate Gram positive organisms from Gram negative. The slide is dried, and then examined under oil immersion. Many clinicians use a semi-quantitative grading (0-4+) system to help quantify organisms; this approach is helpful when following progress by cytology but keep in mind that ear cytology is a crude test and there are many variables that affect the number of organisms counted on cytology.

Acute otitis externa is often characterized by edematous swelling and closure of the ear canal; many dogs are quite painful. A few days of steroid therapy and just about any of the commercial topical products used for 5-10 days will resolve the issue. Still, it is best to make a cytology and try to cater the treatment to what you find. If just bacteria are found, using a product like Cortisporin Otic, which contains polymyxin B, neomycin, and hydrocortisone is useful; I also like Tresaderm for these cases. For yeast only otitis, I like Tris-EDTA with
ketoconazole or a mix of Conofite with Synotic (see recipes below). For very early cases, using EpiOtic Advanced daily for 3-5 days will often arrest the infection before it builds to a significant level. The key to success here is to avoid being parsimonious with the ear medication. It is best to ask owners to fill the ear canals so that we can be sure that medication is reaching the horizontal canal. These cases may not require an extensive search for underlying cause. It is the recurrent and chronic cases that give us our biggest challenges.

Patients with chronic or recurrent otitis externa should have their infection cleared, then a search for underlying causes made before they relapse again. Most dogs with this disorder will relapse until a maintenance ear cleaning program is instituted. I believe every dog with a history of chronic or recurrent otitis should have weekly ear flushes with a good quality cleansing agent. My personal favorites are EpiOtic Advanced (Virbac) and DOUXO Micellar (Sogeval), but I also like the Dermapet line, particularly Malacetic Otic. This product line recently has been acquired by Dechra.

Patients with recurrent or chronic otitis, in addition to cytology, will benefit from culture and sensitivity. This will tell us what organisms are involved and what antibiotic choices we have. Most of these animals may need an anesthetic ear procedure to clean the ears and verify the status of the tympanic membranes. Most of our problem cases involve resistant Pseudomonas aeruginosa or methicillin resistant Staphylococcus spp. (S. pseudintermedius, S. schleiferi). In some cases, dogs have both these difficult organisms!

Otitis externa associated with Pseudomonas aeruginosa is a very difficult problem. These are diabolical opportunistic bacteria that thrive in a moist environment. There are several characteristics that make these infections difficult to treat. First, these bacteria produce endotoxins that are tremendously irritating to the skin, thus substantial swelling and ulceration occur, making it difficult and painful to medicate the ears. Second, they rapidly become resistant to a variety of antibiotics. Third, they produce mucopolysaccharide biofilms that protect the colonies that help resist antibiotic killing. We have developed a strategy for treating these infections that seems to salvage the ear for most of our patients. The key features are oral steroids, thorough cleaning under general anesthesia and high volume liquid topicals.

1. Establish the infection by making cytologies. If gram negative rods are seen, then culture and sensitivity is warranted in order to determine if Pseudomonas is present and what options are available for treatment.
2. Prior to cleaning or treating the ear, consider a 2 week course of oral steroids at 1 mg/kg prednisone or prednisolone divided BID. This opens up an ear canal that is often swollen shut, helps to heal the ulcers, and reduces pain.
3. Anesthetize the dog for a thorough exam and cleaning. We perform CT scans as well to check for bony involvement and/or the presence of masses. If there is extensively bony involvement, then medical therapy is highly unlikely to be effective. A total ear canal with bulla osteotomy/ectomy is then indicated. If the bullae are not abnormal, we proceed with a thorough cleaning using the video-otoscope to direct our exam and cleaning. It is critical to do this anesthetic procedure because most dogs with Pseudomonal infections in the external ear canal have otitis media as well.
4. If culture has not been done and you wish to sample the middle ear, you can use a hard plastic tom-cat catheter. You can puncture the ear drum if it is intact (it usually isn’t!) and flush the middle ear for a culture sample. The syringe is capped and submitted to the lab for bacterial culture and sensitivity.
5. Flush the middle and external ear with sterile warm saline or distilled water. If necessary, Cerumene can be instilled to help loosen up and emulsify the exudates.

6. Instill antibiotics and antifungal agents into the middle ear via syringe and clean catheter. It is safe to put enrofloxacin and miconazole into the middle ear. I like to use 10 mg/ml enrofloxacin in Tris EDTA ear cleaner or TrisEDTA/keto if yeast are also present.

Once the cleaning is done, these dogs usually feel much better. There are a number of topical treatments that can be sent home for continued ear treatment. I usually continue the oral steroids for an additional 2 – 4 weeks, tapering the dose. A very useful topical ear treatment for many dogs with Pseudomonas is high concentration enrofloxacin in Tris EDTA ear wash. Even if the Pseudomonas is reported as resistant, it is important to remember that these sensitivities and resistances are based on achievable blood levels by oral or systemic administration. Putting a high concentration of enrofloxacin directly onto the bacteria can be very effective, especially after the biofilm has been disrupted.

The final concentration is 10 mg/ml of enrofloxacin, so Large Animal injectable Baytril (100 mg/ml) is recommended. It is easy to take a 4 oz bottle of T8 or Tris EDTA and subtract 12 mls; then add back 12 mls of Baytril. This is a 1:10 dilution. I don’t usually add steroid to this, but you can. We generally add injectable dexamethasone so that there are 6 mg of dexamethasone per oz. The instructions to the client are to fill the ear canal twice daily. If yeast are also present, then I make this up in T8/keto.

We do rechecks every 2 weeks and check cytology. For long standing infections we like to obtain 2 negative cytoplologies before we stop treatment. Thus treatment times can vary from 4-12 weeks!

We do not routinely use systemic therapy for these dogs as we have so few options. If the bacteria are sensitive to marbofloxacin, we will use it in cases with otitis media. A recent study showed, though, that most ear isolates are resistant to marbofloxacin compared to skin isolates of Pseudomonas, a high percentage of which are sensitive to marbofloxacin.

Once we are finished treatment, all dogs go on maintenance ear cleaning forever. Currently my favorite is EpiOtic Advanced. It contains a sugar cocktail that inhibits the binding of bacteria and yeast to the skin and in my experience, it really helps to reduce recurrences when used regularly. For those dogs that don’t tolerate the EpiOtic Advanced, you can substitute a product like DOUXO Micellar ear cleaner.

Unfortunately, high concentration enrofloxacin does not always work. Other useful topical remedies for Pseudomonas include amikacin, tobramycin, polymyxin B (contained in Cortisporin Otic), ticarcillin/clavulanate, and ceftazadime. Pretreatment with Tris EDTA or T8 often makes treatment more successful. Amikacin can be added to Tris EDTA or HydroPlus brand of HB101 (available from Webster) to a final concentration of 5 mg/ml. For tobramycin, we generally use the generic eye drops. Here is the way we recommend using ticarcillin/clavulanate: take a 3.1 gm bottle of Timentin and add 26 mls diluent so the final concentration is 100 mg/ml. Freeze in 2 mls aliquots. The working solution is one of these 2 ml aliquots + 18 mls saline. Store in 1 cc syringes and freeze. Thaw and add 1/2 ml to each ear twice daily. Others will take a 6 gm vial and reconstitute with 12 mls sterile water and freeze into 2 mls aliquots as a stock solution. This will be good for 3 months. To make the final concentration, thaw one of these and add 40 mls sterile saline.
Divide into 4 10 ml aliquots and freeze. Thaw one at a time and use for one week. Use 1/4 to 1/2 ml per ear twice daily depending on the size of the dog. Some of our colleagues in England are using ceftazadime. They take one gram of this injectable antibiotic with 16 mg dexamethasone and add it to 100 mls of Auroclens (available from Dechra). We have taken 1 gram and diluted it into 100 mls saline, then added 24 mg (12 cc) dexamethasone. This mix yields 3 oz, and it does not have to be frozen.

A second problem infection is otitis associated with methicillin resistant S. pseudintermedius or methicillin resistant S. schleiferi. Diagnosing this infection often precludes the use of a systemic antibiotic, but we have found topical mupirocin to be very effective. Mupirocin is safe in the middle ear, and is often placed into the middle ear of human patients. We make a mix of mupirocin in HB101 (Hydroplus brand preferred) and have the owners fill the ear canals twice daily. These patients are followed with cytologies as well.

Once the infection with either Pseudomonas or Staph is brought under control, we institute maintenance ear cleaning and work on finding and controlling the underlying cause.

**Useful ear recipes:**
For MRS in the ear: take 1/2 tube of mupirocin, add to a 2 oz squeeze bottle and fill to 2 oz with HydroPlus brand of HB101 (available from Webster). Mix thoroughly. Fill the ear canals twice daily.

For yeast in the ear: take one 2 oz bottle of 1% miconazole lotion, and remove 3-5 mls. Add back 3-5 mls Synotic®. Put several drops in each ear twice daily.

**New Approaches to Otic Treatment:**

**Aqueous gels that polymerize at body temperature: used once weekly**
- e.g. Ketocort-Otic, Tri-Logic
- e.g. custom compounded by several compounding pharmacies; e.g. Thermavert Otic by Best Pet Rx [http://1800bestpetrx.biz/WP/?page_id=374](http://1800bestpetrx.biz/WP/?page_id=374)

**Long duration otics containing florfenicol, terbinafine, plus steroid.**
- e.g. Osurnia®, Elanco, florfenicol, terbinafine, betamethasone in a hydrogel formulation. Clean and dry ear, apply 1 tube to each ear and repeat in 7 days. Provides sustained antimicrobial efficacy for up to 45 days. Reported efficacy of 63.7%. Indicated for susceptible strains of Staphylococcus and Malassezia. Unlikely to work against gram negative infections, particularly Pseudomonas.
- e.g. Claro™, Bayer, florfenicol, terbinafine, mometasone in a clear liquid solution. Only approved single dose treatment for canine otitis externa caused by susceptible strains of Staphylococcus and Malassezia. Provides sustained antimicrobial activity for up to 30 days. Reported efficacy is 72.5%.

**Preventive Ear Care (unproven):**
Otic Armor Veterinary Otic Bandage, All-Accem, applied every 3 months as a preventive treatment

Cameo Otic, PRN Pharmaceutical, herbal remedy used once weekly.
Useful References:

Books

Papers:
MANAGEMENT OF ECTOPARASITES: WHAT’S NEW
Valerie A. Fadok, DVM, PhD, Diplomate, ACVD
Zoetis, valerie.fadok@zoetis.com

Learning Objectives:
1. To be able to develop a flea control program customized to each pet’s medical needs and his/her owner’s preferences.
2. To become familiar with the isoxazoline class of parasiticides, used orally for control of fleas, ticks, and mites.
3. To become familiar with the varying clinical manifestations of canine and feline demodicosis, and what treatments are effective.
4. To understand the rise of avermectin-resistant scabies and alternatives to consider when these cases are identified.

Fleas, ticks, and mites have been around for a long time, but we still have much to learn about these parasites, particularly with regard to their control and the vector-borne diseases that they can transmit. Changing climate, increased feral hosts, and reduced use of toxic environmental insecticides has contributed to population booms in both fleas and ticks. Now more than ever pet owners need quality veterinary advice on how to control these ectoparasites to protect the health of their pets as well as their own health. Our efforts are stymied, though, by the fact that flea control products are now available over-the-counter and many people know very little about the life cycle of these pests and the diseases they can carry. Furthermore, the diversion of veterinary products into the OTC market allows for the misuse of these products, with increased reports of side effects and/or toxicoses and perceived product failures. It is very important that veterinarians provide flea control advice to their clients. This advice can be given in the form of handouts, videos, and referral to some of the great information on line provided by Zoetis, CEVA, Bayer, Elanco, Merck, and Merial. There are videos, downloads, and explanations that are fun for clients. My favorite is “The Dirt On Fleas” a video made by Dr. Michael Dryden, available at the website for Comfortis (http://www.comfortis4dogs.com/about-comfortis/testimonials.aspx). Many of these sites offer email reminder services for clients to help them remember to apply their flea control every 30 days. We can also take advantage of our veterinary technicians as well as our receptionist, but we need to make sure that they understand the flea life cycle and can explain it to their clients. Excellent information is also available about ticks. As one example, Merck has an excellent website for Scalibor (http://www.scalibor-usa.com/), which discusses tick control and has user-friendly videos as well as tools to identify ticks. Finally, excellent information for clients and veterinarians is available at Dr. Michael Dryden’s website (http://www.drmichaeldryden.com/); he has excellent videos of questing ticks, as well as downloadable handouts and a link to the video “The Dirt on Fleas.” Additional sites include http://www.vectrapet.com for videos about life cycles and how Vectra 3D works, and http://www.petparents.com/show.aspx/products/advantage-ii-for-dogs/flea-fun-facts.

Fleas
We have some differences in the way we approach dogs and cats with flea infestations compared to those with flea allergies. With regard to infestations, there are some basic facts that the client needs to know and some myths that need to be busted. The major flea infesting the dog and cat is Ctenocephalides felis, and like many insects, it undergoes metamorphosis. The female flea feeds on blood in order to lay eggs, and under ideal
conditions she can lay 50 eggs per day. Adult fleas spend their lifetime on their host, but the flea eggs will roll off into the environment where they hatch into larvae, pupate, and then emerge as adults. The life cycle is variable and dependent on environmental conditions as well as the availability of hosts. For every one flea seen on the pet, there are many more in the environment in the form of eggs, larvae, and pupae and control measures have to address not only the fleas seen on the pet but those remaining in the environment. We know these facts, but most clients don’t. Because they don’t, they have unrealistic expectations about flea control and make poor decisions about how to use it.

There is much talk about flea resistance to the products we use for flea control; however, most of this is perception not fact. It is very true that fleas have become resistant to older insecticides such as organophosphates or carbamates, but it is yet to be proven that fleas have become resistant to fipronil, imidocloprid, or selamectin. In most cases, failure of flea control is due to one or more of the following reasons:

1. The product is not being used every 30 days throughout the year.
2. Flea control products are not being used on all the dogs and cats in the household.
3. The flea control products are not being applied directly to the skin correctly and at the right dose.
4. One tube of flea control is being used on more than one animal.
5. Our pets are being exposed to other dogs or cats who have fleas and who are not being treated with flea control products regularly. In particular, many people will feed feral or semi-feral cats in their yards, which encourages the accumulation of eggs, larvae, and pupae in that yard in protected places.
6. Our pets are being exposed to fleas from wildlife. It has been shown that possums can carry up to 1000 fleas per animal! A significant source of fleas are feral cats, populations of which are increasing in many urban areas. Many of these animals are nocturnal and may or may not be appreciated by the pet owner.
7. Pets are being exposed to fleas in areas under porches, in sheds, or under trees where the wild vectors may congregate at night!
8. Unreasonable expectations: no flea product we use, whether oral or topical, will truly repel fleas, although there may be some repellency associated with permethrin. It can take anywhere from 30 minutes to 24 hrs for a flea to die, depending on what product is used and the time after application. Some products disable the flea from effectively feeding before they die, which is why good flea control helps pets that are allergic to flea saliva. If flea control is not used until adult fleas are seen, it will take 8-12 weeks to get rid of fleas in the environment, as they complete their life cycle and become adults. So, the fleas that are seen today are not the same fleas that will be seen tomorrow.

We can help reduce the length of time it takes to get good control by using integrated pest management particularly when we have heavy infestations; this involves excellent flea control on all pets in the household as well as the use of environmental treatment. In order to break the flea life cycle, we choose adulticides that kill
fleas so rapidly they don’t live long enough to lay eggs, or we can utilize the products that contain insect growth regulators as well as adulticides.

What about the flea surge? Each part of the country that supports fleas will have times at which the flea numbers increase greatly. For my part of the country, numbers of fleas surge in the spring and again in the fall. These are times at which the climate is perfect for flea growth and reproduction.

Flea allergy is special! How many times have we heard from our clients (especially for indoor cats) that fleas cannot be the cause of the skin disease because they never see fleas. That is the time to pull out the flea comb and see what can be found. But it is important to know that failure to identify fleas or flea dirt is not proof that fleas are not the cause of dermatitis. Flea allergic pets are expected to have fewer fleas or flea dirt than nonallergic pets because they do so much grooming. The best way to rule out flea allergy is by response to treatment. Capstar® (nitenpyram) is one of the most effective flea control products we have and the killing effects of one dose persist for 48 hrs. A Capstar® trial can be used in both dogs and cats to determine the role of fleas in pruritus. Capstar® can be given every other day for one month. If fleas are the sole cause of the itch, the pet will be dramatically improved, and a regular flea control program can be started that will work for them. With the advent of the oral products with prolonged activity (spinosad, isoxazoline), Capstar® trials may not be necessary.

The best source of information about parasiticides can be found at the CAPC website. You can download a PDF for those used in dogs, and one for cats as well (http://www.capcvet.org/resource-library/). We do not need to review each of these, but we can make a few comments about specific products. There are two ways to approach flea control: orally or topically. The appearance of spinosad (Comfortis®, Trifexis®) revolutionized flea control for many allergic pets, because these animals often need frequent bathing. In addition, many clients prefer the oral route because they don’t like the smell or the appearance of the coat after topical products are applied, they have observed topical drug eruptions, and/or they are concerned about transfer of the chemical to their children. Spinosad is labeled for use every 30 days and should be given with food to maximize absorption and reduce vomiting. Lufenuron, present in Program® and Sentinel® remains a great product and I have used Sentinel® combined with Comfortis® because we then get both adulticide and insect growth regulator activity. We see quite a few clients that utilize Sentinel® as their sole flea control; it is important to remind people that there is no adulticide activity in this product.

The appearance of the isoxazoline class has really revolutionized flea and tick control, and offers a striking new treatment for mites as well! Afoxolaner (Nexgard®, Merial) is given every 30 days by mouth, and provides excellent flea and tick control. It can be given with or without food and is approved for use in dogs of 8 weeks of age or older. Fluralaner (Bravecto™, Merck) also provides excellent flea and tick control. It is given every 3 months with food; if Lone Star tick is of concern then every 2 months is recommended. Bravecto is approved for use in dogs 6 months of age or older. The newest entry into the isoxazoline class is sarolaner (Simparica™, Zoetis). This compound was synthesized in the laboratories at Zoetis, and has been shown to kill fleas within 3 hrs and ticks within 8 hrs, with persistent efficacy for at least 35 days. It is effective whether given with food or not, and is approved for use in dogs 6 months of age or older. These isoxazoline compounds kill fleas very rapidly, and can eradicate infestations on dogs in approximately 2 weeks.
The other route for flea control involves topical administration. The efficacy of most topical products may be affected by frequent dermatologic bathing, although we believe that good killing can persist for 21-30 days when bathing is done weekly with a non-stripping shampoo. Reduced efficacy would have major effects on those pets allergic to fleas. Our old standbys such as fipronil (Frontline® products, Merial) and imidacloprid (Advantage™ products, Bayer) remain excellent products, but it is worthwhile noting that compared to Advantage, Advantage Multi™ (imidacloprid with moxidectin, Bayer) has improved efficacy against fleas (data from Dr. Byron Blagburn), and it provides excellent heartworm protection as well as efficacy against several mites. It can be useful in dogs with mild to moderate demodicosis when used weekly, and in some cats with Demodex gatoi if used every other week for 3 months. Another useful multifunctional product is Revolution® (selamectin, Zoetis). If used every 30 days it provides excellent flea control for cats and dogs, and when used every 2 weeks off label is great for treatment of sarcoptic mange, cheyletiellosis, and ear mites. It is NOT effective against Demodex mites in dogs or cats. Vectra® (dinotefuran and pyriproxifen) and Vectra 3-D® (dinotefuran, pyriproxifen, and permethrin) from CEVA have been useful to us in Texas, particularly along the coast where Culicoides and mosquitoes may contribute to skin disease. Similar results have been seen in Florida, where Culicoides hypersensitivity may be more common in dogs (personal communication, Dawn Logas). We have had several successes with Vectra-3-D® in dogs that did not do well with Comfortis, and its permethrin may help provide some tick control as well. Alternatives could include the Scalibor® collar, containing deltamethrin, from Merck, and the Seresto® collar, containing imidacloprid and flumethrin from Bayer, which provide flea and tick protection.

Fleaborne diseases potentially transmissible by C. felis to humans include cat scratch fever (Bartonella henselae), other Bartonella spp., murine typhus (Rickettsia typhi), flea-borne spotted fever/cat flea typhus (Rickettsia felis), plague (Yersinia pestis), and the tapeworm Dipylidium caninum. It is disturbing to note that 58% of stray cats can be positive for Bartonella spp, and up to 90% of the fleas that infest them positive. Fortunately, the prevalence in pet cats is much lower (3%). In addition to causing anemia in cats and dogs by blood loss, C. felis also carries Mycoplasma spp which cause anemias in cats (M. haemominutum, M. haemophilus).

**Canine demodicosis**

Canine demodicosis has traditionally been divided into juvenile and adult onset forms, as well as localized and generalized form. It is commonly accepted that the tendency to develop juvenile generalized demodicosis is an inherited trait, and for that reason we recommend against breeding these dogs. We also recognized that when females come into estrus, demodicosis can relapse; ovariohysterectomy is therefore recommended not only to prevent breeding but to help control the disease. Adult onset demodicosis is recognized commonly, and we often find an underlying cause to include immunosuppressive therapy, endocrinopathies such as hypothyroidism and canine Cushing’s disease, any systemic or metabolic disease, and neoplasia. But not all dogs with adult onset demodicosis have an identifiable underlying cause; we recognize in some breeds (e.g. the Shih Tzu) the tendency to develop adult onset demodicosis. In particular we recognize the development of deep pyoderma in the feet which responds to antibiotics but relapses. These dogs are rarely curable, so they require maintenance mitecidal therapy for life.

Why dogs develop generalized demodicosis remains poorly understood. We still don’t completely understand the immune response to these mites, or the influence of local factors in the skin that regulate their growth. It is
suspected that both humoral and cell mediated immunity contribute to mite control. There is an association between mite overgrowth and production of anti-inflammatory cytokines such as TGFbeta and interleukin-10; these cytokines have suppressive effects on the immune system, and treatment has been shown to reduce their levels.

We have always believed that all dogs have Demodex mites, albeit in low numbers, but it has been difficult to demonstrate by skin scrapings or hair plucks from normal dogs. Recently though, this belief was corroborated by using real time PCR from material associated with plucked hairs. These experiments confirmed that mites do live in very low numbers in normal canine skin. BUT when we find even one mite on skin scraping, it likely suggests clinical relevance and disease.

Three mite types have been described in the skin of dogs. The traditional follicular mite is Demodex canis. A long-tailed mite Demodex injai has been described that is often associated with dorsal greasy skin in terrier dogs, and a short tailed mite, called Demodex cornei, that is found together with D. canis in some dogs. Recent analysis by PCR has shown that while D. injai appears to be a novel species, D. cornei is actually a morphologic form of D. canis, the follicular mite.

Diagnosis of demodicosis is most commonly made by deep skin scrapings, but hair plucks are very useful particularly around the eyes and feet. Several hairs are plucked and placed in mineral oil; the slide is examined as we would for a deep skin scraping. Occasionally biopsy may be necessary when lesions are fibrotic (e.g in the feet) and for the Shar Pei. It is important to note that skin scrapings are rarely negative if they are done correctly; capillary ooze is what we are hoping to achieve. In contrast to scabies, we do not do treatment trials to rule out demodicosis when we don’t find mites.

Treatment options for demodicosis in dogs are varied. The only approved treatment is amitraz dips (Mitaban®, Zoetis). Most clinicians use oral ivermectin daily, achieving a final dose of 0.4 to 0.6 mg/kg/day. Several breeds of dog, including the Collie, have a mutation in an efflux pump (MDR-1) that increases their sensitivity to the drug. A PCR-based test is available at Washington State University to determine if dogs carry this gene (http://www.vetmed.wsu.edu/depts-VCPL/test.aspx); this website gives the breeds of predisposition and the percentages of dogs in that breed that carry the gene. If the results are reported at normal/normal, ivermectin can be used, even in Collies. We still recommend stepping up the dose slowly though as ivermectin toxicosis has more than one mechanism. It is critical to avoid the use of spinosad when using high dose ivermectin, as it precipitates ivermectin toxicosis. We are often asked when we can restart the spinosad after stopping the ivermectin. A good rule of thumb is about 5 half lives; our toxicology friends suggest 10-14 days should be helpful. And if you want to use ivermectin, wait 2-3 weeks after stopping the spinosad.

Other treatments include injectable doramectin given weekly by subcutaneous injection, oral moxidectin given daily, oral milbemycin given at 2 mg/kg/day, and topical moxidectin applied weekly in the form of Advantage Multi™. This is an off-label used, and seems to work best in dogs with low numbers of mites and mild demodicosis.

One of the most exciting new findings is the efficacy of fluralaner, afloxalaner, and sarolaner for the treatment of demodicosis. One paper has been published about fluralaner (Bravecto™, Merck), and one for sarolaner
(Simparica™, Zoetis), but we are rapidly accumulating evidence that afoxalaner (Nexgard®, Merial) is also very effective. Bravecto™ given orally every 2-3 months, or Nexgard® or Simparica™ given every 30 days seems to provide a very rapid kill of Demodex mites. Recently a publication verified the ability of sarolaner (Simparica™) to kill Sarcoptes also. For dogs that need long term mite control, using these products according to label may well prevent relapse while controlling fleas and ticks!

**Feline demodicosis**

Cats have a follicular mite, Demodex cati, and a surface mite Demodex gatoi. Recently a third mite has been identified by PCR, but its role in skin disease has not yet been identified. Demodex cati, the hair follicle mite, has been identified as a cause of chin acne, particularly in older cats, and it can sometimes be found within the ear canals of cats with ceruminous otitis externa. In these cases, there may be no identifiable underlying cause. Some cats treated with inhalation steroids have developed localized demodicosis on the muzzle. More extensive infestation with D. cati has been associated with serious systemic diseases (neoplasia, metabolic disease) or retroviral infections. More commonly we see the short tailed mite, D. gatoi, as a cause of hair pulling in cats, particularly on the abdomen. Diagnosis of D. gatoi is made by skin scrapings, but it is not always possible to find the mites. It may be helpful to do a fecal exam. We have also found it helpful to do skin scrapings on the unaffected cats in the household as they seem to carry more mites. Because we can’t rule out D. gatoi on the basis of negative skin scrapings, therapeutic trials are recommended. Key historical clues include a poor response to steroids, a history of a new cat in the home, and/or a cat that goes outside. This mite is not sensitive to selamectin or other routine methods of flea control. The treatment of choice has been weekly lime sulfur dips for 6-8 weeks, but this treatment is not effective in all cats. In my practice, many cats will respond to the use of Advantage Multi™ applied every 2 weeks for 3 months; the moxidectin is the active ingredient.

**Updates on Sarcoptic Mange**

Sarcoptic mange is easy to diagnose in its classic form (young dog with crusting on the ears, elbows, body with demonstrable mites), but it is important to consider this mite in older dogs as well. We don’t always find the mite with skin scrapings, so it is important to rule out this possibility by treatment. My suspicion is raised when I see an older allergic dog that suddenly has a relapse of severe itch. Skin scrapings in these patients are often negative, so a treatment trial is warranted.

I usually recommend selamectin (Revolution®) or imidacloprid/moxidectin (Advantage Multi™, Bayer) for treatment, asking the owners to apply it every 2 weeks for 3 treatments. This will provide flea control as well, which is important in many parts of the country. It is important to note that avermectin resistant scabies has been identified; there is one case report in Japan but we are identifying these cases in some areas in the USA. For those dogs, treatment options could include amitraz dips, lime sulfur dips, and weekly Frontline sprays.
However, with the recent report that sarolaner (Simparica™, Zoetis) is effective against Sarcoptes, the isoxazolines could become the treatment of choice for canine scabies.

REFERENCES