Atopic Dermatitis: The New Paradigm and How it Changes the Way We Treat It
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The understanding of canine atopic dermatitis (cAD) has changed dramatically over the last several years. This has lead to a change in our therapies. It is now accepted that the pathogenesis of cAD involves not only an immunologic component but also a barrier dysfunction. This disruption of normal barrier function leads to increased allergen penetration and sensitization. Thus, the therapeutic approach has changed from addressing only the immunologic abnormality (hypersensitivity) to one that also includes managing the barrier dysfunction. It is essential that before treatment for cAD is begun that the proper diagnosis has been established. It is recognized that the diagnosis of cAD is a clinical diagnosis made by ruling out other pruritic diseases\(^1\). Criteria that can help establish a diagnosis of cAD are\(^2\):

1. Onset of signs under 3 years of age
2. Dog living mostly indoors
3. Glucocorticoid-responsive pruritus
4. Pruritus sine materia at onset (i.e., alesional pruritus)
5. Affected front feet
6. Affected ear pinnae
7. Nonaffected ear margins
8. Nonaffected dorso-lumbar area

If the dog meets 5 criteria- there is a specificity of 79% (21% false positives) and a sensitivity of 85% (15% false negative).

If the dog meets 6 criteria- there is a specificity of 89% (11% false positives) but the sensitivity decreases (more false negative) to 58% (42% false negative).

In the author’s experience an easier and very accurate modification can be used as follows. It is called the “One minute atopic dermatitis test”. If you have a pruritic dog you can be fairly certain that he/she has cAD ectoparasites and infection (bacterial, yeast/fungal) have been ruled out. There are exceptions to the rule but they are very uncommon and suspicion for these diseases would be raised based on signalment, history and physical findings. Note that serum testing/intradermal testing and/or food trials may be needed to ID flare factors of cAD but are not used to diagnose cAD. Whether these additional tests are necessary depends on the severity of the cAD.

Treatment of the pruritic dog:
There are a variety of therapies for the symptomatic relief of pruritus in dogs with atopic dermatitis which will help the disease at that moment. These treatments will do nothing to prevent recurrence, this can only happen if the underlying cause is identified and treated. You will be more effective long term in treating the pruritic patient if you find the “due to” rather than just treat the symptom (pruritus). This lecture is focused on new therapies for the treatment of cAD.

If a specific diagnosis for the pruritus has not been established after the initial diagnostic tests have been performed and infection is present it is best to treat the infection for 14-21 days and then re-evaluate how much pruritus remains. DON’T use GC, oclacitinib or lokivetmab. Treat what you know and see what is left. If you used the previously listed drugs and also the infection at the same time it would make interpretation of response to therapy impossible (was it the antipruritic drug or the antibiotic/antifungal therapy that resolved the pruritus?).

If the pruritus has resolved after only treating the secondary infections and/or ectoparasites it means that the ectoparasites or the secondary pyoderma/Malassezia dermatitis was the major trigger of the pruritus at this time. This secondary infection was due to one (or more) of the following:

1. Ectoparasites
2. Seasonally triggered environmental allergen induced atopic dermatitis and the season has changed
3. Nonseasonally triggered environmental allergen induced atopic dermatitis that is not symptomatic when the infection is absent (threshold theory)

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4. Environmental allergen induced atopic dermatitis that is triggered by a cutaneous food reaction that is not symptomatic when infection is absent (threshold theory)

5. An endocrinopathy (hypothyroidism, hyperadrenocorticism)- remember these are only pruritic when there is a secondary bacterial infection or Malassezia overgrowth.

If pruritus continues after treating the secondary infections and a specific primary disease has not been not been established through physical examination and laboratory testing, or there was not a secondary infection to begin with the next step is a therapeutic ectoparasitidal treatment (if it has not been previously performed). Glucocorticoids or oclacitinib may be used during the first week or 2 of the ectoparasitidal treatment but they need to be stopped a couple weeks before rechecking so that it can be determined whether it was the medication or the ectoparasitidal treatment that resolved the pruritus. If the pruritus has continued in spite of treating for infection and ectoparasites a food trial should be instituted. A home cooked diet is the gold standard and owners should be encouraged to use this diet rather than commercial diets. It is beyond the scope of this lecture to discuss the many reasons that this is true but to summarize the high point- commercial foods contain ingredients that are not labeled. In addition commercial diets have only been shown to have a 50% negative predictive value (poor at ruling out the disease).

Both the diet trial and a therapeutic ectoparasitidal treatment can be done simultaneously. If they are done simultaneously and there is a positive response you can do a food “challenge” to determine which therapy was effective. By going back and feeding the original diet and seeing if the pruritus resumes you will be able to determine the underlying cause. A short course of GC or oclacitinib at the beginning of the therapeutic trial may be done as long as you have eliminated the presence pyoderma, Malassezia, demodex and dermatophytes.

At the end of these steps, if the pruritus has resolved w/o the concurrent administration of GC or oclacitinib, you have identified your primary cause and can treat accordingly. If the dog has residual pruritus then the dog has environmental triggered atopic dermatitis.

**Treatment of canine atopic dermatitis- overview**

As previously mentioned it is now recognized that canine atopic dermatitis has both an allergic component and a barrier dysfunction component both of these should be addressed in your treatment.

**Treatment options for dogs with atopic dermatitis include -** (please note that these therapies are used as a preventative so they should be instituted before clinical signs recur):

1. Good skin care
   a. Restore barrier function
   b. Protecting the skin
      i. Wiping the dog off after coming in from outdoors
      ii. Clipping the hair coat to a short length (10 or 15 blade) which helps to decrease exposure to and contact with environmental triggers (allergic and irritant).
      iii. Clothing all the time and boots outdoors
   c. Bathing with a hypoallergenic veterinary shampoo that contain moisturizers or barrier repair ingredients (eg shampoo that contain phytosphingosine) weekly
   d. Follow the bath w/a humectants or barrier repair product
      i. In humans moisturizers are best applied w/in 2 minutes after finishing the bath for maximum effect
   e. Fatty acid supplementation- try an omega 3 product for 3 months and if there is no improvement, try a product with a combination of an omega 3 and 6
      i. Omega 3
      ii. 18 mg/kg of EPA daily
      iii. Omega 6/3- double the bottle dose OR
      iv. High fatty acid diets
   f. Bathing is helpful to decrease antigen load and bacterial colonization

2. Identify and prevent/manage the triggers (ectoparasites, food, infection (bacterial/Malassezia))
   a. If the dog has environmental triggered atopic dermatitis, allergen specific immunotherapy (ASIT) is appropriate if the symptoms are present for more than 2 or 3 months/year and is severe enough to need corticosteroids or cyclosporine for symptomatic control. ASIT may be administered either subcutaneously or sublingually. See comments at the end of this article
   b. If the dog has a food trigger- avoid those foods
   c. Good flea control especially if the dog has flea bite hypersensitivity

3. During acute flares- treating infection and inflammation is necessary. Therapy would include antibiotics, antifungals and glucocorticoids along w/the above recommendations

4. Treatment options for symptomatic relief of dogs w/atopic dermatitis w/o secondary infection are
   a. Glucocorticoids
Advantages – quick, effective against both pruritus and inflammation including ear canal disease, inexpensive. Appropriate for short term use or when finances restrict other options

Disadvantages – numerous – well known

b. mCSA

i. Advantages-

ii. The author uses this drug in dogs with uncomplicated atopic dermatitis if the dog is moderately to severely pruritic and I want to avoid steroids (due to side effects or owner preference) and has failed to respond to oclacitinib

iii. There may be a 4-6 week delay before seeing full effectiveness so you can give glucocorticoids during the first 3 weeks to help keep the dog comfortable during this lag time.

iv. Side effects in dogs are very limited and are primarily GI. Other side effects reported include cutaneous papillomatosis and hyperplastic gingivitis. In order to minimize the most limiting factor of CSA (vomiting) I use Cerenia® or zofran (0.5-0.75 mg/kg) 30 minutes before administering mCSA. I do this for the first 4-7 days and administer Atopica® with a meal.

v. An important drug interaction is ketoconazole (KCZ). KCZ inhibits the enzyme responsible for CSA metabolism (cP450 3A4) thereby increasing concentrations and prolonging elimination of CSA. Because of the cost of CSA, coadministration with ketoconazole has been used by some authors in DOGS. This combination with KCZ can lower the amount of CSA that needs to be administered. Doses suggested are 2.5 mg/kg of CSA and 7.5 mg/kg of KCZ sid. Please note failure to respond to this combination doesn’t mean that a full dose of CSA will be ineffective. The author therefore rarely begins therapy w/this combination. Note recently the author has seen resistant cutaneous Malassezia infections. Is this due to the indiscriminate use of KCZ orally and topically?

vi. Dosage is 5 mg/kg sid on an empty stomach. There may be a 4-6 week delay before seeing full effectiveness so you can give GC during the first 3 weeks to help keep the dog comfortable during this lag time.

vii. Side effects in dogs are very limited and are primarily GI. Other side effects reported include cutaneous papillomatosis and hyperplastic gingivitis. In order to minimize the most limiting factor of CSA (vomiting) I use Cerenia® for the first 4 days and administer Atopica® with a meal.

viii. Drug interactions – the most important is ketoconazole (KCZ). It inhibits the enzyme responsible for CSA metabolism (cP450 3A4) thereby increasing concentrations and prolonging elimination of CSA. You need to be aware of this when treating Malassezia with KCZ if the dog is also on CSA

ix. You can use this drug interaction to your advantage by using a combination of CSA and KCZ using 2.5-5.0 mg/kg of CSA and 5-7.5 mg/kg of KCZ

c. Oclacitinib

i. During inflammation, a variety of mediators such as cytokines, chemokines, and neuropeptides are released into the microenvironment by Th2 lymphocytes. (note in dogs w/AD there is an increase in the number of Th2 lymphocytes) Cytokines convey their information by binding to specific receptors on the cell membrane to induce a biologic response. The cytokine receptors are transmembrane receptors composed of multiple subunits. On the intracellular portion of each receptor subunit are one of 4 JAKs – JAK1, JAK2, JAK3 and TYK2.

ii. Afferent nerves, in close proximity to the inflammation that are responsible for pruritus are activated by these mediators. They transmit signals that travel along unmyelinated C nerve fibers and are received by the dorsal root ganglia (DRG) within the dorsal horn of the spinal cord. The signal finally reaches the brain and affects regions involved in pruritus. Adjacent afferent nerves are stimulated (axon reflex) when the peripheral nerve endings of the affected area release neuropeptides (e.g., substance P, calcitonin gene-related protein, CGRP) and neurotropins (e.g., NGF). These mediators can also modulate inflammatory responses as well as directly triggering vascular responses in the skin. In the skin, cytokines regulate acute and chronic processes such as neuronal itch stimulation and inflammation.

iii. After a cytokine binds to its cell membrane receptor it triggers specific intracellular pathways. One such intracellular pathway is the Janus kinase (JAK) pathway. Cytokines implicated in allergic skin disease (such as Interleukin IL-31 and IL-4) bind to their receptor on the cell membrane and activate the JAK pathway. JAKs activate intracellular proteins called Signal Transducer and Activator of Transcription (STAT) to induce gene transcription and biological responses.
iv. What types of proteins or functional changes are produced by activation of the AK/STAT pathway?
Some are 1) ↑ IgE production 2) lymphocyte proliferation 3) ↑ cytokine production 4) cytokine receptor expression 5) ↑ chemokine production 6) pruritus

v. Oclacitinib is a JAK inhibitor with more selectivity to block JAK1 than JAK2, JAK3 or TYK2. It blocks the activation and function of cells that use the JAK1 enzyme as a part of the cytokine receptor. The result is a decrease in the activity of pro-inflammatory and pruritogenic cytokines that use JAK1 such as IL-2, -4, -6, -13, -31.

1. The organ systems that are affected by the inhibition of JAK1 mainly are the epidermis, lymphocytes and the peripheral nervous system.
2. Inhibiting JAK1 inhibits the production of IL 31. IL31, which is made principally by activated Th2-type T cells, induces production of several chemokine involved in inflammatory skin disease. These chemokines are not only involved with inflammation but also recruit to the skin IL 31 producing T cells thereby amplifying inflammation and pruritus.
3. IL 31 receptors are also present on nociceptive neurons in the dorsal root ganglion. Currently it is unclear whether IL 31 induces pruritus by directly modulating the function of sensory neurons or stimulating keratinocytes, which may induce a yet unknown keratinocyte-derived mediator that subsequently activates unmyelinated C fibers in the skin.

vi. In a review of 200 dogs treated in the author’s practice, the drug was effective in adequately controlling pruritus in about 75% of the dogs with environmental induced atopic dermatitis when used per label instructions.

vii. The dosage is 0.4-0.6 mg/kg bid x 14 then sid. Some dogs will have their pruritus increase when the dose is changed from bid to sid. Before adjusting the medication be sure to collect your minimum data base to evaluate for bacterial pyoderma, Malassezia dermatitis and ectoparasites. If the dog has uncomplicated atopic dermatitis and sid oclacitinib is inadequately controlling the pruritus the author will do the following step wise adjustments

viii. If the dog is not responding at all (or minimally) to sid then increase the dose if possible (the chart accompanying the drug has a some dogs receiving the low end of the dose while others are at the high end).

ix. If the above doesn’t work and you have not used modified cyclosporine you should do so

x. Regardless of the response to oclacitinib – identifying and treating the underlying cause is the best course of action rather than just masking the symptoms.

xii. Because this drug blocks the neurogenic component of pruritus other pruritic skin diseases (pyoderma, flea allergy, scabies) may also respond to this medication. This emphasizes the importance of a thorough dermatologic examination and a minimum data base of skin scrapings and cytologies. Pruritic dogs, whether or not they are given oclacitinib, should have flea control therapy instituted.

xiii. The author is concerned cases may not have a thorough evaluation before dispensing oclacitinib and that dogs may have these other pruritic diseases present but not addressed. The author will dispense oclacitinib in the same situations as mCSA except if the dog needs instant, predictable relief, mCSA would not be appropriate due to the lag effect, while oclacitinib would be effective. Before dispensing oclacitinib the author discusses the following with the owners

1. Identifying and treating the underlying cause is the best long term therapy
2. The author has used this drug for 6 years with no serious side effects noted.

d. Lokivetmab (Cytopoint) is an injectable formulation containing a caninized monoclonal antibody (mAb) against interleukin-31 (IL-31). These mAb remains in circulation for several weeks. It exerts a therapeutic effect by binding to and neutralizing soluble IL-31, thus inhibiting pruritus and reducing skin lesions. Like other naturally-occurring antibodies and antibody-antigen complexes, elimination is via normal protein degradation pathways.

i. It is administered by a subcutaneous injection and is repeated monthly, as needed.

1. Some dogs may need it less than every 30 days
2. May be effective even in dogs that failed to respond to oclacitinib

ii. It is for DOGS only
iii. Long term safety and efficacy has yet to be determined. One of the issues is will dogs develop antibodies to the product since it not 100% canine autobody (contains 10% mouse).

1. To reduce immunogenicity in dogs recombinant DNA technologies are used to engineer the antibodies to be over 90% canine in structure

   e. Antihistamines/tricyclic antidepressants – there are a variety of antihistamines available that may help mildly pruritic dogs.

5. ASIT
   a. May be administered either subcutaneously (SCIT) or sublingually (SLIT)
   b. SCIT
      1. Has a long term track record of safety and efficacy
         a. Will see less severe reactions that need injection modification (localized swelling, increase in pruritus, etc)

6. SLIT
   a. Recently sublingual immunotherapy (SLIT) has become available to veterinarians for the treatment of canine atopic dermatitis (cAD). The author has some reservations about the use of this therapy for cAD.

Recognizing that SLIT has been used for many years in Europe for the treatment of human asthma we can review the information that is available in that species. The vast majority of studies and protocols in humans are for rhinitis/asthma and NOT atopic dermatitis. A review in human medicine (2006) found the following –
   i. Dosing summary
      1. The studies included doses that varied by 30,000-fold
      2. Frequency of dosing varying from daily to weekly
      3. Duration of treatment varying from 2 months to 5 years

Their conclusion was that SLIT is an effective treatment (for rhinitis or asthma) but it was unclear what the proper dose, treatment schedule and overall duration of treatment was to be effective.

Other review articles found that the cumulative monthly dose varied between 0.017 and >500 times the customary subcutaneous maintenance dose. In addition that each manufacturer uses its own standardization, formulation, and administration schedules. In a review of SLIT for human atopic dermatitis the authors could only find 1 double blinded, placebo controlled randomized study (DBPCR). That study evaluated the efficacy and safety of SLIT using house dust mite containing drops. They concluded that for mild–moderate disease there was significant improvement but there was no improvement in cases of severe disease. But it went on to say that standardized treatment was essential to ensure therapeutic efficacy. They used 80 umg protein concentration/day once daily with instructions for the patients to keep the drops under the tongue for 1–3 minutes and then swallow. Note in this study the treatment group had a total efficacy rate of 77.78% (cured + marked improvement) vs. 53.85% in the control group. These were statistically significant but look at the placebo effect! The other important finding was that during the first year of immunotherapy there was no difference between placebo and SLIT response and the difference was only noticeable at 2 years. In 2015 there was a systematic review to evaluate the evidence supporting the use of SLIT for hAD. They could only find 5 studies to fit their criteria. They found that in 4/5 studies there was an improvement in AD but in 2/4 there was a substantial placebo effect making the true effect of SLIT difficult to determine. They found serious shortcomings such as lack of control group, lack of randomization and data analysis was not by intention to treat. The group graded 1 of the studies to have moderate quality, 2 to have low quality and 2 to have very low quality.

As you review the studies in veterinary medicine concerning SLIT and eAD you will note that all studies except for 1 have the same very serious limitations- they are open studies, there are no placebo groups and the studies only applies to mite sensitive dogs. Also the studies state that there are statistically significant changes in CADESI and PVAS but doesn’t state if this translated into CLINICAL improvement- for example pruritus may go from +10/10 to a +7/10- which may be statistically different but not clinically different. In the 1 DBPCR study that has been done to date in veterinary medicine, they found that overall the percentage of dogs that improved >40% were 50% in the control and 66% in the active group. Once again look at that placebo response! Two problems with this study- 1 they don’t state if the response rate is statistically different and also the criteria that has been establish states there must be at least a 50% improvement in pruritus to be considered clinically significant- so why did that study use a 40% cutoff?

Lastly, things that give the author great pause about this whole subject is that there are some companies that refuse to tell the veterinarian what is in the SLIT formula that they expect us to give to our patients. In addition the different antigen companies are using different strengths in their SLIT (one company offers a dilution of 20,000 pnu or 40,000 pnu whichever you want – but doesn’t give guidelines how to chose), different volumes and different frequency (sid vs bid). So how can they all be effective? Discussion about dermatologist who formulate their own SLIT in their hospitals also reveals a lack of standard protocols. The author uses SLIT in very limited, specific situations such as when owners are absolutely adamant that they won’t give SCIT and won’t bring the pet in.
for you to give the injection, an animal that has had a severe reaction to SCIT or if the animal fails to respond to SCIT after 1-1 ½ years. I tell the owner that we really don’t know how successful this method is but that it is very safe to try.

Summary from the ACVD task force on AD

Treatment of acute flares of canine atopic dermatitis
1. Identification and avoidance of flare factors:
   a. Identification and elimination, whenever possible, of allergenic flare factors (fleas, food and environmental allergens)
   b. Evaluation of use of antimicrobial therapy if clinical signs of infection or colonization with bacteria or yeast are present on the skin or in the ears
2. Improvement in skin and coat hygiene and care:
   a. Bathing with a nonirritating shampoo
3. Reduction of pruritus and skin lesions with pharmacological agents:
   a. Treatment with topical glucocorticoids, especially for localized lesions, as needed to control signs
   b. Treatment with oral glucocorticoids, especially for widespread or severe lesions, as needed to control signs

Treatment of chronic canine atopic dermatitis
1. Identification and avoidance of flare factors:
   a. Dietary restriction-provocation trials in dogs with nonseasonal signs
   b. Implementation of an effective flea control regimen in areas where fleas are present
   c. Performance of allergen-specific intradermal and/or IgE serological tests to identify possible environmental allergen flare factors
   d. Possible implementation of house dust mite control measures, if relevant and feasible
   e. Evaluation of use of antimicrobial therapy if signs of infection or colonization with bacteria or yeast are present on the skin or in the ears
2. Improvement in skin and coat hygiene and care:
   a. Bathing with a nonirritating shampoo or an antiseborrheic/antimicrobial shampoo, depending on the skin lesions seen
   b. Dietary supplementation with essential fatty acids
3. Reduction of pruritus and skin lesions with pharmacological agents:
   a. Treatment with topical glucocorticoids or tacrolimus, especially for localized lesions, as needed to control signs
   b. Treatment with oral glucocorticoids, cyclosporine or subcutaneous interferon, especially for widespread or severe lesions, as needed to control signs. These agents would not normally be combined together.
   c. Use of steroid-sparing agents, such as essential fatty acids, Chinese herbs and antihistamines, if glucocorticoids are being used as a long term treatment option.
4. Implementation of strategies to prevent recurrence of signs
   a. Avoidance of known flare factors, as identified above
   b. Consideration of preventive pharmacotherapy, if feasible and relevant
   c. Implementation of allergen-specific immunotherapy, if feasible. This can be used alongside all the above treatment options in an attempt to provide long term amelioration of the aberrant immune response
5. When should you consider antihistamines, steroids, cyclosporine, Oclacitinib, lokivetmab, ASIT, SLIT for the pruritic atopic dog without infections (should of course do good skin care and flea prevention as mentioned above)
   a. Each of the treatments have advantages and disadvantages which I will try to summarize below
   b. Antihistamines/EFA
      i. I would use in mildly pruritic dogs
      ii. Safe, inexpensive, available OTC
      iii. No age restrictions- very few contraindications

iv. Possibly effective in mildly pruritic dogs
v. No advantage of using second generation antihistamine (eg Loratidine)
vi. For optimal efficacy, this class of drugs are best used as preventatives before a flare occurs—not during or after it—and they should preferably be given on a continuous daily basis.

c. Steroids
   i. I would use if limited budget and the dog has seasonal symptoms without concurrent infection
      1. Appropriate for acute flares of uncomplicated atopic dermatitis (pruritus only)
   ii. Inexpensive, rapid onset and very effective
      1. Only drug effective for decreasing the swelling in ear canals
   iii. Should have cbc, serum chemistry profile and a urinalysis if on steroids for >6 months
   iv. May be effective for managing otitis
   v. Effective as a transition drug during the lag phase of CSA or the lag phase of ASIT/SLIT
   vi. Numerous short term and long term side effects
      1. Oral and topically administered steroids are also detrimental for the epidermal barrier due to multiple mechanisms including decreased lipid synthesis, decreased epidermal proliferation and differentiation and decreased production of antimicrobial peptides.

d. Cyclosporine
   i. Consider if Oclacitinib is ineffective and the dog is a chronic steroid dog or doesn’t tolerate steroids
   ii. Long track record of use
   iii. No age restrictions
   iv. Can be used concurrently with steroids
   v. Can be used in diabetics
   vi. Effective in 50-60% of the cases
   vii. Because of the slow onset of action
      1. Need to have concurrent steroid or Oclacitinib for the first 3 weeks or so
      2. Slow onset of action of makes them unsuitable for managing acute flares of AD
   viii. Relatively safe-can predispose to gingival hyperplasia and systemic fungal infections (rare).
      1. Predisposes to papillomas
   ix. May cause GI side effects- especially initially — use cerenia or zofran for first week or so
   x. If on >6 months, should have cbc, serum chemistry profile q 6-12 months depending on dosing and frequency of administration
   xi. May be expensive if needed in large breed dogs — at full dose daily
      1. May be able to decrease frequency of administration to q 48 hrs or even 2 times weekly
      a. May be able to lower the daily dose if less frequent administration is not adequate
   xii. Ineffective in treating or preventing otitis

e. Oclacitinib
   i. I use if a dog needs instant relief and I am trying to avoid steroids (preparing for IDT, hx of chronic steroids, etc)
   ii. If I am going to treat an elderly dog who has atopic dermatitis (not enough time for ASIT to be effective)
   iii. Labeled for allergic dermatitis not just environmental allergen induced atopic dermatitis
   iv. If I am going to treat a dog long term with symptomatic therapy only
   v. Rapid onset, minimal side effects
   vi. Can be used in diabetics
   vii. Can be used prn for pruritus
   viii. More expensive than steroids
   ix. Limited long term studies but appears to be well tolerated
      1. Predisposes to papillomas

x. Weight gain w/o polyphagia or change in caloric intake
   1. May be because of inhibiting STAT -
      a. In humans, STATs tend to promote lipolysis in mature adipocyte—so inhibiting
         STAT will prevent lipolysis
xi. Ineffective for treating or preventing otitis
   1. Should not be used in animals <12 months of age, or pregnant or lactating animals
xii. May not be effective when administered sid
f. Lokivetmab
   i. For dogs where owners can’t/won’t give oral medication
   ii. For dogs that need instant relief and steroids or olacitinib is contraindicated (pyoderma, demodicosis, age, etc.) or has been ineffective
   iii. Rapid onset
   iv. No age restriction
   v. Can be used in combination with any other therapy
   vi. Parental administration= no need for owner to medicate
   vii. Minimal side effects but limited time frame
   viii. ONLY label for atopic dermatitis
   ix. Expensive especially in large dogs
   x. Needs to be repeated every 14 (off label) to 60+ days
   xi. Ineffective for treating or preventing otitis
g. ASIT
   i. Safe, long track record
   ii. Can cure/long term remission
   iii. Avoids oral administration
   iv. However, owners need to learn to give injections or take the dog to the veterinarian
   v. Can prevent otitis, pyoderma and recurrent Malassezia
   vi. Can be used in combination with any other therapy
   vii. Maybe more expensive than other options
h. SLIT
   i. Consider if the dog has had a reaction to ASIT, owner has needle phobia or dog has failed ASIT
   ii. Safe
   iii. May be effective in cases where ASIT failed
   iv. No good EBM studies documenting effectiveness
   v. No long term studies
   vi. Has to be administered sid or bid
Canine Cutaneous Adverse Food Reactions: Diagnosis and Treatment
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Initially, the ACVD task force on canine atopic dermatitis (cAD) defined cAD as a genetically-predisposed inflammatory and pruritic skin disease, most commonly associated with IgE antibodies to environmental allergens. cAD has now been recognized as a multifaceted disease associated with exposure to various offending agents such as environmental and food allergens[7]. This author believes that the later definition should be used when discussing cAD.

It is important to remember that there are many other causes for pruritus in the dog other than cAD[8] such as ectoparasites, cutaneous neoplasia (epitheliotropic lymphoma), bacterial pyoderma, etc. so canine pruritus is not always due to cAD.

In veterinary medicine the criteria for diagnosing cAD has evolved over time. Historically 1 of 2 sets of criteria have been used for making the diagnosis of cAD[9,10]. The problem with these previous criteria is the former was never validated while the later had a limited sample size. The most current guideline was proposed by Favrot[11]. Please note that before applying these criteria to a pruritic dog, other causes of pruritus, such as ectoparasites or infectious causes, need to be ruled out. You shouldn’t use these criteria alone to make a diagnosis of cAD. History, physical examination, diagnostic testing and response to treatment should also be included in your evaluation.

The criteria used to establish a diagnosis of cAD include
1. Onset of signs under 3 years of age
2. Dog living mostly indoors
3. Glucocorticoid-responsive pruritus
4. Pruritus sine materia at onset (i.e. alesional pruritus)
5. Affected front feet
6. Affected ear pinnae
7. Nonaffected ear margins
8. Nonaffected dorso-lumbar

Using these criteria, if 5 criteria are matched, and ectoparasites and infectious causes have been ruled out, the sensitivity and specificity are about 85% and 79% respectively. This means that using only this criteria, a wrong diagnosis will be made about 20% of the time.

Once you have established a diagnosis of cAD it is important to identify triggers that may cause the cAD to flare up. Triggers include
1. Environmental allergens
2. Food allergens
3. Ectoparasites
4. Infectious (bacterial, Malassezia)

This lecture is going to focus on food allergens as the trigger.

Food allergy (FA) is recognized as a potential cause of various dermatological and gastrointestinal (GI) signs in the dog and cat. The exact incidence of FA is unknown. However, the term “allergy” is often used indiscriminately. Acquaintance with exact terminology is important when dealing with FA.

An adverse food reaction (food sensitivity) as defined by the American Academy of Allergy and Immunology and the National Institute of Allergy and Infectious can be divided into two categories: immunological and non-immunological reactions. Food allergy (food hypersensitivity) implies an immunological reaction following food intake. Food intolerance (FI) is due to a non-immune mediated

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reaction. Food idiosyncrasy, food toxicity, food poisoning, anaphylactic food reaction, pharmacological and metabolic food reactions are all forms of FI.

Cutaneous clinical signs of an adverse food reaction (CAFR) are identical to that of environmental triggered cAD. The only clue that the dog may have a CAFR is that there MAY be GI signs present. In regards to an environmental trigger, the only definitive clue is if the dog has a history of seasonal symptoms.

An elimination diet trial (EDT) is the ONLY diagnostic tool that is useful in dogs with suspected adverse reactions to food. In vitro testing, biopsies, intradermal skin testing and gastroscopic food sensitivity testing are not reliable for diagnosing FA. Be aware that an EDT doesn’t give any information about the underlying immunologic mechanism. Although FI can also be identified with an elimination diet it is generally accepted that most of the animals with adverse reactions to food do suffer from FA if cutaneous signs are present.

The first step in performing an EDT is to identify 1 protein and 1 carbohydrate that the dog has not previously eaten and feed that to the dog for 60 days. No other food, treats, flavored medications, etc should be fed during the EDT. The dog is then re-examined 30 and 60 days after beginning the EDT. If symptoms resolve, the dog is then “challenged” with his original diet, expecting exacerbation of the pruritus within 14 days if the dog has CAFR. If symptoms recur within 14 days of feeding the original diet, the dog should be fed the EDT once again and the symptoms should resolve.

What diet should be used to diagnosis CAFR? The choices are a commercial novel protein, a hydrolyzed limited antigen or a home cooked diet. A diet can only be “hypoallergenic” if the animal was never exposed to the food components before. The identification of what is truly a novel protein for any given individual is determined by a very detailed dietary history. Because of the enhanced complexity of pet foods, it has become more difficult to compose a suitable elimination diet.

Regardless of what type of diet is used to diagnose CAFR there are a number of potential pitfalls to avoid. A common mistake made during food trials is using flavored heartworm preventative. This was reported in an abstract12 in which there were 12 dogs with natural occurring CAFR to either soy or corn. The author fed a flavored heartworm preventative (Interceptor) fed to each dog. This preventative contained pork liver and soy. A clinical score (CS) was assigned based on the severity of skin and otic disease. After 1 pill 10/12 dogs had an increase in CS. In 5/12 dogs the values peaked on day 2 post challenge while in 5/12 dogs it occurred on day 5.

Another problematic is the use of supplements or medications during the food trial. In a study the authors tested 7 supplements for the presence of soy, pork, or beef antigens13. Three were flavored OTC products and 4 were veterinary therapeutics. All OTC test products produced ELISA results in agreement with their ingredient lists. ELISA testing of veterinary therapeutic products did not agree with either their ingredient lists or product inserts because of the presence of other ingredients not listed. In 1 product the “artificial beef flavor” was made using pork liver and 1 arthritis product listed “natural flavors” which was determined to be a spray-dried digest derived from pork liver. Another potential problem identified was administering supplements/medications that were in a gelatin capsules. This is because the gelatin is derived from beef or pork. This lead the authors to recommend that veterinarians contact manufacturers of oral therapeutics prior to prescribing them during a dietary elimination trial to determine the other ingredients in those products that may not be listed on the ingredient list or product insert.

Mislabeling is not limited to supplements. A study14 was done using 12 dog foods (eleven novel protein diets and one hydrolyzed diet) from five different manufacturers, both international and Italian, for potential contamination by animal origin ingredients that were not mentioned on the label. The food was analyzed using both the official method (microscopy to identify bone fragments of different zoological classes (mammalian, avian and fish) and by polymerase chain reaction (PCR) for the identification of DNA of animal origin. In 2/12 samples the results of both analyses match the ingredients listed on the label. In the remaining 10 samples, microscopy detected bone fragments from 1 or 2 unlabeled zoological classes. In 6/10 samples there were undeclared avian fragments. 5/10 had fish and 4/10 had mammalian fragments. In two samples, microscopy analysis identified a contamination that would have otherwise passed unobserved if only PCR had been used. However, PCR identified the DNA of undeclared zoological class in 2 samples. The conclusion of the authors was that dogs might fail to respond to commercial limited antigen diets because such diets are contaminated with potential allergens. Both PCR and microscopy analysis are required to guarantee the absence of undeclared animal sources in pet foods. Lastly a study by Okuma et al collected 52 commercial dog and cat food products from southern California and on line. They tested the foods for the presence of eight meat species (bovine, caprine, ovine, chicken, goose, turkey, porcine, and equine) using real-time polymerase chain reaction (PCR).15 Of the 52 products, 31 were labeled

correctly, 20 were potentially mislabeled because they either (1) contained meat species that were not included on the product label (16) and/or (2) did not contain meat species that were included on the product label (7) - note some food had both problems. One food contained a non-specific meat ingredient that could not be verified. Pork was the most common undeclared meat species detected. There was also a trend to substitute lower cost ingredients, such as poultry meats, for higher cost ingredients, such as beef and lamb. These studies support the position that before ruling out an AFR, a novel protein home-made diet trial should be performed.

A retrospective study added additional evidence to support the statement that a homemade diet is superior to commercial diets in diagnosing CAFR. In this retrospective study reporting CAFR in cats, the author evaluated cases presented to a dermatology referral service for possible CAFR. Seventeen cats were diagnosed with having CAFR. Home prepared elimination diets were completed by 16 cats; 8 cats with a final diagnosis of CAFR failed to respond to a minimum 6-week commercial hydrolysed protein diet but did respond to the home-made diet. Of the 13 cats in which their final dietary management was reported, 6 cats could not tolerate any commercial dry foods, but did tolerate select canned foods; 7 cats were able to consume commercial dry foods, with 4 maintained on commercial hypoallergenic diets and 3 with other commercial restricted protein diets.

As previously discussed, an appropriate elimination diet should contain 1 new, highly digestible protein or a diet that contains hydrolyzed proteins. Ideally a homemade diet (HMD) should be fed. This is the type of diet the author uses. A HMD consists of one novel protein and one novel carbohydrate. The protein usually is rabbit, venison, goat, ostrich, emu or alligator. White or sweet potatoes, oats, quinoa or rutabaga are appropriate carbohydrate sources. It is mixed 1 part meat and 3 parts carbohydrate and the dog is given 1-2 cups of the mixture/10#. HMDs should not include ANY other ingredients. The dog must not ingest any other food, treats, tidbits, etc including items used to hide medication in. Avoiding gelatin capsules should be attempted. This may be difficult because some medications only come in a capsular form (e.g. modified cyclosporine). The problem with HMDs is that they are nutritionally inadequate for growth and maintenance therefore they are not using in growing dogs or for long term maintenance. Because they are not very calorically dense most animals will lose weight on these diets. If a dog has a body score of 4/9 or less, this author does not use a HMD.

Although a HMD is not nutritionally balanced nor complete, supplements are not necessary, nor used, during the short test period. When a HMD is given during a prolonged time, it is recommended to consult a veterinary nutritionist to formulate a balance diet.

Although the gold standard for diagnosing CAFR is a HMD there are circumstances where the author will use a commercial diet instead. Examples include owners who will not cook for the dog, if the dog doesn’t tolerate HMDs (typically because of weight loss but some dogs will become lethargic on them or have GI disturbances). They are not fed to growing dogs.

Commercial novel protein diets (NPDs) can be used to diagnosis CAFR and also can be used long term to maintain a dog with CAFR. A variety of NPDs are available for dogs. These diets are readily available but do not have a 100% negative predictive value (false negatives occur 25-50% of the time). A number of studies have demonstrated the problems associated with NPD. In the first study they fed dogs with proven CAFR either venison/rice, chicken/rice or catfish/rice commercial dog food. When fed the venison dog food 85% of the dogs with CAFR reacted while 52% and 47.5% reacted to chicken and catfish dog food respectively. More recently 3 of 4 over the counter (OTC) dog foods that didn’t list soy on their ingredients list had soy identified via ELISA testing. More disturbing was the study that reported 3 out of 4 OTC dog foods that specifically stated “NO SOY” had soy found when ELISA testing was performed. Note that in the same study 2 of 3 hydrolyzed soy diets had intact soy identified.

Commercial hydrolyzed protein diets (HPDs) contain proteins that been enzymatically hydrolyzed to smaller molecules. This reduces the MW of the original protein which leads to a decrease in the antigenicity and allergenicity of the protein. This means that the molecules are too small to evoke a cross binding between IgE on the surface of the mast cell. This prevents degranulation of the mast cell and IgE-mediated (Type I) hypersensitivity. This is a key point because if the CAFR in that dog is not caused by IgE (which is believed to be the more common scenario) but by some other mechanism (e.g. type IV which is a T cell driven disease) the size of the molecule doesn’t matter and the diet will be ineffective. The optimal MW of a protein hydrolysate in dogs has not been agreed upon. Hand et al states that an ideal molecular weight of less than 10,000 Daltons, while Cave states that if the protein size is reduced to less than 6,000 Daltons in size, it should reduce binding to IgE and increase digestibility. However, Verlinden et al states that peptides over 4,500 Daltons could still be capable of starting the immunologic reaction which contributes to the allergic reaction. In addition these diets are only partially hydrolyzed. This means that only a percentage of the protein is hydrolyzed- there is still some intact protein remaining. In the humans, peptides with a MW as low as 3000 Da are still capable of an allergic reaction. Free AA are not allergenic, but

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are not suitable in foods because of their bitter taste, high osmolality (leading to diarrhea) and very high costs. As with the NPD, HPD are not able to diagnose CAFR in all dogs; they probably miss about the same percentage as the NPD.

Regardless of which diet is used there are a few points to discuss. The first issue is how long to feed the diet. The following is based on the best evidence available as of December 14, 2014 and is information gathered from 209 dogs with CAFR. After 3 weeks on the diet approximately 50% of the dogs will have achieved a complete or marked reduction (>50%) of pruritus. After 5 weeks 85% of dogs had responded partially or completely and by 8 weeks >95% had responded. Less than 5% needed 9-13 weeks. Information gathered from 40 cats with CAFR revealed that it took approximately 4 weeks (50% of the cats), 6 weeks (80%) and 8 weeks (90%) on the diet to achieve a remission. As in dogs, by 13 weeks 100% had either partially or completely responded. Remember if at any point the pruritus has completely resolved, the diet can be “challenged” at that time, there is no need to extend the special diet any further.

Veterinarians are frequently asked by owners which ingredients cause the most reactions? The answer depends on the study. In 265 dogs reported collectively by 12 different studies, beef, dairy products, and wheat accounted for two thirds of reactions. Reactions to corn, pork, rice, and fish were rarely reported in dogs. In the April 2013 issue Veterinary Dermatology a letter to the editor reported the most common ingredients causing CAFR in 330 dogs- beef, dairy, chicken and wheat accounted for 78% of the reactions. Of 56 cats reported collectively by 10 studies, beef, dairy products, and fish accounted for 80% of reactions.

More recently a literature search (limited to 1985-2015) for canine or feline food allergy in CAB Abstracts and Web of Science revealed that of the 297 dogs included in the selected studies the most frequently reported food allergens involved in dogs were beef (102 dogs, 34%), dairy products (51 dogs, 17%), chicken (45 dogs, 15%), wheat (38 dogs, 13%) and lamb (14, 5%). Other less commonly reported offending food sources were soy (18 dogs, 6%), corn (13 dogs, 4%), egg (11 dogs, 4%), pork (7 dogs, 2%), fish and rice (5 dogs each, 2%). In cats the food sources most frequently causing CAFR in were beef (14 cats, 18%), fish (13 cats, 17%), chicken (4 cats, 5%), wheat, corn and dairy products (3 cats each, 4%) and lamb (2 cats, 3%). Egg, barley and rabbit were also reported as offending allergens in individual cats.

The problem with any of these retrospective studies is that the offending allergens listed reflects pet feeding habits in the preceding decades, and these allergens could change once new pet foods become fashionable and used more frequently. Note that many owners believe that food additives (dyes and preservatives) are common causes of food allergy in dogs, yet there has not been even 1 published case report documenting this.

Maillard reactant products are formed when proteins are cooked with carbohydrate. They can increase or decrease the allergenicity of proteins, depending on the food component. This phenomenon may explain the apparent increase in allergenicity of proteins in commercial pet foods compared to fresh proteins. Because of this, the author suggests that when preparing the HMD the protein and carbohydrate should be cooked in separate pots.
Protocols are useful in helping to diagnose and treated many different disorders. Part of any good protocol should be a minimum data base (MDB). In addition to signalment, history, etc in veterinary dermatology, laboratory testing should be a component of this data base. Just as you may have a standard set of tests for diarrhea you should have a standard set of tests for dermatology cases. Because practitioners get busy, sometimes collection of this minimum data base is overlooked. By training technicians to perform the tests this potential problem can be avoided. Instructing technicians to perform these tests on every pruritic animal ensures that this will be done on every case.

Tests can be separated into immediate and delayed tests. For a pruritic dog or cat all the immediate tests should be performed. Which of the delayed tests should be performed will vary based on the results of these tests.

Immediate tests include
1. Skin scrapings **
2. Impressions smears **
3. Ear cytologies ** if ear disease is present
4. Fine tooth combing **
5. Hair plucks/trichograms

Delayed tests would include
1. Skin biopsies
2. Woods lamp and fungal culture
3. Bacterial culture and susceptibility
4. CBC, serum chemistry profile and urinalysis
5. Adrenal function tests
6. Thyroid profile
7. Dietary elimination food trial
8. Intradermal testing (or serum testing) and allergen specific immunotherapy

** Component of MDB

Equipment
The equipment needed is very basic and include
1. #10 scalpel blade - dulled by scratching the frosted part of a glass slide
2. Mineral oil
3. Frosted glass slides and cover slips
4. Clippers
5. Microscope
6. Minitip culturettes
7. Needle and syringes
8. Woods lamp +/- derm duet
9. Punch biopsy
10. Lidocaine/bupivicaine/sodium bicarbonate

Skin scraping
Let’s begin with skin scrapings. Before performing skin scrapings you should ask the following questions
1. What technique do I use (broad superficial or deep scrapings or both)
2. Where do I need to skin scrape?
3. What lesions should be scraped?

The answers to these questions depend on which parasite you suspect. If you suspect a superficial mite (Sarcoptes, Notoedres, Demodex gatoi (cats), Demodex cornei (dogs) Cheyletiella) then broad superficial scrapings should be performed. Deep skin scrapings should be performed when Demodex canis or catti is suspected. (Table 1)

When performing superficial scrapes be sure to scrape from appropriate areas. For Sarcoptes you will be more successful if you scrape pinnal edges, the elbows, ventral chest and hocks. In addition any popular, crusted or erythematous lesion should be scraped.
For any of the superficial mites, broad scraping should be performed. Remember that mites associated w/hypersensitivity (eg Sarcopetes, Cheyletiella) may be difficult to find due to their low numbers so be sure to take multiple (10-15) sites. In contrast to demodex, all scrapes can be placed on 1 or 2 slides because the quantity of mites present is not important, they are either found or not.

When performing a deep skin scrape for demodex (this applies mostly to dogs) there are a few pitfalls to avoid. By avoiding these errors the diagnosis and your management of demodex will improve.

These include
1. Failure to squeeze the skin prior to scraping. Squeezing helps express the Demodex from the hair follicles
2. Failing to record location of scrapes;
3. Failing to record numbers & stages present;
4. Failing to record whether the mites are alive or dead;
5. Failing to clip hair at skin scrapings sites (if it is a recheck appointment, the hair may be regrowing preventing proper sample collection);
6. Failure to squeeze the skin prior to scraping to try
7. Failure to recognize that lesions that are granulomatous & fibrotic, especially on the paws may have demodex that are hard to demonstrate on skin scrapings and a skin biopsy may be necessary to diagnosis;
8. Failure to sedate dogs if the feet are to be scraped
9. Failing to scrape hyperpigmented areas even if they are not alopecic;
10. Failing to scrape areas with comedones even if they are not alopecic
11. Failing to scrape if a dog only has greasy seborrhea (especially along the dorsum). A long body type of demodex mite has been identified (Demodex injai). This mite lives in the sebaceous glands of the dog's skin, and thus, is commonly associated with "greasy coats" rather than the moth eaten or pustular appearance that we are used to seeing.
12. Failing to take broad superficial skin scrapes even if demodex is the only parasite you suspect. There is a short bodied demodex mite (Demodex cornei), which lives on the surface of the skin layer. Note that there may be a low number of these mites found because of the superficial location of the mites allowing removal by the animal.

Cytology
Cytologic examination is another very commonly performed procedure in dermatology that should be performed on any dog or cat presented w/skin or ear disease. Cytology is used to identify the presence (and/or type) of:
1. Bacterial or fungal organisms (Malassezia);
2. Neoplastic cells;
3. Inflammatory cells;
4. Abnormal cells (eg acantholytic keratinocytes associated w/pemphigus foliaceus)

When the skin is scaly, a superficial skin scraping can be useful. A very small amount of mineral oil is placed on a #15 scalpel blade to help keep the scale on the blade once it has been collected. The lesion is scraped a few times, and the material collected is placed on a microscope slide, stained (see below about staining samples), and examined microscopically at 40X and 100X.

Direct smears can be collected by a variety of ways.

Impression (touch) smears are useful when there is an erosion, ulcer, crust, moist or greasy lesion. To perform an impression smear, a slide is firmly applied to a lesion and, in most cases, is then gently moved back and forth a few times to increase the yield. Some people will use slides that are “sticky” on one side. These slides are reported to increase the yield of sample collected but the author finds that a standard slide works quite well. The slide is then processed and examined as described below.

If the lesion is fluid filled (eg pustule, papule) but is too small for a fine needle aspirate, “lance” the lesion with a 25 gauge needle, gently squeeze the lesion and then do an impression smear of any material expressed. When sampling crusts, lift the crust and rub both the underside of the crust and the surface of the skin.

Roll smears (swabs) are used when it would be difficult to get a slide into the affected area. This could be the face fold, the interdigital space on cats and small dogs and the ear canals in all dogs and cats. A cotton tipped applicator is gently rubbed back and forth across the lesion and then the material from the applicator stick is rolled back and forth on the slide. If the lesion is scaly, applying a small amount of mineral oil to the swab can help with collection. The sample is rolled onto a microscope slide, stained and examined as previously described.

A fine needle aspirate is performed when a solid or fluid filled mass or lesion is present. A 22-25 gauge needle attached to a 12 cc syringe is placed into the lesion and suction is applied by pulling back the plunger of the syringe (1/2 to 3/4 of the way). The syringe plunger is pulled back and released a few times. Don’t aspirate aggressively enough that you get blood contaminating the sample (you should not see blood in the hub of the needle). After aspirating one spot, stop aspirating and redirect the needle in the mass w/o pulling out and repeat the aspiration. This can be repeated 2 or 3 times on each sampling attempt. The needle is disconnected from
the syringe, the syringe is filled w/air and the needle is placed back on the syringe. The material is then ejected from the needle by compressing the plunger. If the lesion is a fluid filled you only have to pull back far enough to get a sample into the syringe. Note-

Regardless of the collection technique (except when using the tape prep) historically the author would heat fix the sample, using a cigarette lighter, and then wait a minute or so to allow it to cool. The slide was then stained w/a modified Wright stain (Diff Quik®). There are 3 jars in the Diff Quik® kit. The first jar is a fixative containing methanol, the second contains buffered xanthene dye, which stains the cells and organisms red and the third contains a buffered thiazine dye (methylene blue) which stains the cells and organisms purple. After drying, the slide would then be examined.

A more rapid and equally effective method is to bypass both the fixative step and the second step (eosin) and directly go to the 3rd step using the methylene blue only. It doesn’t appear to hinder the identification of bacteria, yeast or inflammatory cells except for eosinophils. If using the tape prep I will put a drop on stain on the slide and then place the tape, sticky side down, over the stain and examine.

Ear cytologies are performed to identify mites, infectious agents and inflammatory cells. A cotton tip applicator is used to collect the samples prior to instituting therapy. Results of the cytology help direct appropriate therapy (presence of infectious agents would indicate the need for antimicrobial therapy). I will also perform ear cytologies during therapy if either the ear(s) are not responding to treatment OR if there were rods or WBC’s on the initial cytology regardless of the appearance of the ear. If the initial cytology revealed yeast and/or cocci and the looks normal at the recheck examination I don’t cytology it since I don’t expect to sterile the ear canal- in fact the treat for eliminating certain bacteria (eg enterococcus) may be just discontinue the antibiotic and allow restoration of the normal microbiome.

A few tips when examining your sample.

1. For skin cytologies
   a. For bacteria look in 10 fields and record a range (eg 0-5, 5-10, 10-20 etc) – be sure to note if they are cocci or rods, if WBC’s are present or not and if the bacteria are intracellular or extracellular
   b. For Malassezia look in 20-25 fields (unless they are ID sooner). Report them as negative/+0 if NO Malassezia is found, +1 if 1 or 2 organisms are found (total #) in all the fields examined and there were never more than 1 in a field, report a +2 if there are more than 1 organism in a field or 1 organism q 3-4 oil fields – treat any case w/a +2 and consider treating even if +1. In fact the ACVD now recommends either reporting Malassezia as either present or absent.

2. For ear cytologies
   a. There is no universal agreement as to what are normal number of cocci or Malassezia from an ear cytology
      i. Because the host reaction to the organism is as important as the number, ANY organism seen in a diseased ear will be treated as part of the therapy regardless of the number present
   b. Inflammatory cells or rod shaped bacteria are never present in a normal ear.

Fine tooth combing
Combing of the hair with a fine tooth comb (“flea comb”) is a method that can be useful in finding fleas and other ectoparasites (ticks, lice and Cheyletiella). You may also detect military lesions on cats that were not appreciated on your physical examination.

Trichogram (“hair plucks”)
Veterinarians are frequently presented w/animals that have hair loss. In establishing the diagnosis of the hair disease, signalment, history (constitutional signs present or not?) and physical examination (eg pot belly, enlarged liver, etc) are important components in establishing a diagnosis. There are times that even w/this information the cause of the alopecia has not been established. A trichogram, which is a microscopic evaluation of plucked hairs, may be a useful tool to help identify the underlying cause.

If the alopecia is post traumatic (pruritus) or due to fragile hairs (eg dermatophytosis) the distal end of the hairs will be broken (or if the dog/cat gets haircuts). If the hair loss is spontaneous (eg endocrinopathy) the tips are tapered.

Hair plucks can also be useful in ruling in (but not ruling out) demodicosis. Other ectoparasites may also be identified such as Cheyletiella or lice.

Follicular cast can also be identified w/hair plucks. Follicular casts refers to the accumulation of keratin debris that adheres to the hair shaft as it extends out of the hair follicle. This finding indicates a follicular keratinization disorder which occurs w/vitamin A responsive dermatosis (rare- but if occurs would be a Cocker Spaniel most likely), follicular infections (demodex, dermatophyte, bacterial), Malassezia dermatitis/sebaceous adenitis, endocrinopathy (hyperadrenocorticism, hypothyroidism) or primary seborrhea such as ear margin seborrhea.
Skin biopsies
Skin biopsies are an easily performed outpatient procedure. The author will perform a skin biopsy for:

1. Any skin disease that is not responding to what should be effective therapy;
2. Any skin disease that may be potentially neoplastic;
3. Any skin disease that may be a cutaneous marker for a systemic disease (eg hyperkeratotic footpads associated with metabolic epidermal necrolysis);
4. Any skin disease that may be autoimmune or immune mediated;
5. Any nodular disease;
6. Any skin disease that appears unusual;
7. Any skin disease that requires expensive or potentially toxic therapy

The 2 methods used to biopsy the skin are the punch technique and the elliptical, incisional biopsy.

For punch biopsies, the author usually will use a 6 mm punch biopsy instrument. When using this instrument, DO NOT include normal tissue in the sample- only the lesion. If biopsying the edge of a lesion then perform an incisional biopsy.

The author uses elliptical, incisional biopsy with a scalpel blade for lesions that are alopecia, ulcerated, erosive or are suspected to involve the subcutaneous tissue (eg panniculitis). For subcutaneous lesions, a punch sample may not get subcutaneous tissue and therefore may miss important lesions. This type of biopsy has one end of the sample in normal tissue and 1 end in the middle of the abnormal. The biopsy should be elliptical and request the laboratory to section the sample from tip to tip. This technique allows the evaluation of the formation of the lesion- from normal to very affected skin- it allows a “story to be told” about the lesion.

Sites should NOT be shaved or scrubbed prior to collection since this may remove very valuable information. The hair may be partially clipped to visualize the lesion better, but in order to avoid traumatizing the skin, at least ¼ inch length of hair should remain.

Bacterial cultures
In the past, bacterial cultures were not frequently performed in dogs with skin disease since Staphylococcus intermedius was the most common bacterial pathogen and had a predictable susceptibility profile. Unfortunately it isn’t that simple any more. Staphylococcus intermedius, Staphylococcus pseudointermedius, Staphylococcus lugdunensis or Staphylococcus delphini Staphylococcus schleiferi subsp. Schleiferi, Staphylococcus schleiferi subsp. coagulens, and Staphylococcus aureus all w/variable susceptibilities (methicillin resistant, multidrug resistant, combination) are now associated w/pyoderma in dogs. The need for bacterial culture and susceptibility testing in the dog or cat has become more frequent. Indications for bacterial culture would include the presence of:

1. Nodules;
2. Deep draining tracts;
3. A bacterial infection of the skin (confirmed by identifying intracellular bacteria and degenerative neutrophils) that fails to respond to appropriate antibiotic therapy;
4. Suspicion of an uncommon bacterial infection (atypical mycobacteria, nocardia, actinobacillus);
5. Suspicion of an anaerobic infection (gas pocket formation);

A few tips when dealing w/a bacterial culture (see table 1 for more details)

1. Use a Mini-Tip Culturette (Becton Dickinson Microbiology Systems) to pin point the sample
2. Taking samples from 2 or 3 lesions (if possible) will increase the likelihood of identifying all pathogens
3. Do cytology concurrently
4. When selecting a lesion to culture – from best to worst - pustule >papule>crust>epidermal collarette
5. If you are sampling a crust- lift the crust and swab the underside of the crust and the surface of the skin under the crusts with a the culturette.
6. For an epidermal collarette- lift the edge of the collarette- if you are not able to do this then clip the hair w/scissors to expose the collarette then take a the culturette swab and gently roll it across the collarette 3 to 4 times.
7. Have the lab do susceptibility testing use the tube dilution (MIC) rather than disc diffusion (Kirby-Bauer)

Wood’s lamp examination and fungal culture for dermatophytes
Dermatophyte infection is a common problem in cats and young animals of all species. Proper collection of the specimen is critical in identifying this infection. The first step is to examine the animal with a Wood’s lamp. You should let the Wood’s lamp warm up for at least 10 minutes, and then shine the light on the hair coat looking for apple-green glow to the entire hair shaft. Remember crusts may glow as may some topical medications. A positive test is suggestive of dermatophytes, but you need to culture the hair to confirm this. Please note that a negative test does not rule out dermatophytosis, in fact you should only use the lamp to guide in selecting hairs to pluck for culture not as a tool to rule out dermatophytosis.
Prior to collection, the suspected skin lesion should be gently cleaned if grossly contaminated. Mild soap (not antimicrobial) and water may be used. Allow the site to dry before collecting the sample. Using a sterile hemostat, you should pluck the hairs near the base so that you can get close to the bulb. Also scrape a small amount of scale/crust from the edge of the lesions. This will increase the success rate of identifying dermatophyte infections. If there are diffuse lesions or you are screening a cat for infection, a Mackenzie toothbrush method is used. To perform the toothbrush method, take a sterile toothbrush and rub it over the entire lesion from the margins to the center. Then take a sterile hemostat and remove the hairs/scale from the toothbrush and inoculate the culture plate.

Once a media is inoculated, close the cover and place the culture plate in a plastic bag or “pencil box” with a sponge to prevent dehydration of the media which can inhibit growth of organisms. In contrast to previous recommendations the sample does not need to be placed in a darkened area and it doesn’t need to be incubated—it should be left at 77-86°F. PUT IT IN A PLACE WHERE IT WILL BE EXAMINED DAILY.

If submitting to a reference lab, just take the sample and place it in a red top tube and send that to the reference lab. If you are doing the culture in house, be sure to check it DAILY and record the findings. It is important to note when the media changes color w/respect to colony growth. A large amount of growth w/small color change (contaminant) is interpreted differently than a small amount of growth & large color change to RED (dermatophyte). The color of colony is important in determining contaminant vs. dermatophyte, as is microscopic examination of macroconidia. To get the sample for microscopic examination, apply sticky side of clear acetate tape to the culture media where the growth has occurred. Then stain the sample with Lactophenol cotton blue. By microscopically examining the sample you can speciate the dermatophyte. By speciating the dermatophyte you can tell the source of the infection (see below). This is done by identifying macroconidia. The descriptions of the different macroconidia are available in many textbooks or on line.

Table 1. Sampling techniques for lesions of superficial bacterial folliculitis for bacterial culture and susceptibility testing

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Sampling procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pustule</td>
<td>No surface disinfection. Clip hair with sterile scissors (avoid clippers). Lance pustule with sterile narrow-gauge needle. If purulent exudate is visible on the needle, apply to a sterile swab; if not, gently touch exudate expelled from pustule with sterile swab and place in transport medium or sterile container. Sometimes lancing of very small pustules results in haemorrhagic exudate, which is still suitable for sampling.</td>
</tr>
<tr>
<td>Crust</td>
<td>No surface disinfection. Use sterile forceps or a sterile needle to lift the edge of a crust. The presence of exudate under a crust indicates an ideal site for culture. Touch sterile swab to exposed skin surface and place in transport medium or sterile container.</td>
</tr>
<tr>
<td>Epidermal colarette</td>
<td>No surface disinfection. Clip hair with sterile scissors (avoid clippers). Roll sterile swab across border of colarette two or three times and place in transport medium or sterile container.</td>
</tr>
<tr>
<td>Papule*</td>
<td>Sampling by biopsy is probably more reliable. Provide local anaesthesia by subcutaneous injection of 2% lidocaine. Clip hair with sterile scissors or clippers. Clean skin surface by a single wipe with 70% alcohol (no additional surgical preparation). Allow alcohol to dry. Using a sterile 3 or 4 mm punch and sterile surgical instruments, collect tissue sample and place in sterile container or transport medium. Suture biopsy site. Alternatively, papules may be prepared and disinfected as above, then sampled by insertion of a sterile needle and culture of emerging or expressed blood or exudate.</td>
</tr>
</tbody>
</table>

*There is no research to show which method is more appropriate. †This method of disinfection is suggested to kill any surface bacteria. However, there is no research to indicate the value or necessity for any disinfection of the skin surface prior to sampling of papules.

Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis
Superficial bacterial folliculitis (SBF) is one of the most common dermatologic problems diagnosed in dogs. The infecting organism is usually a staphylococcus. In the past, successful treatment could be accomplished with a beta lactam antibiotic (a first generation cephalosporin (eg cephalaxin) or a potentiated amoxicillin). Increasingly, methicillin resistant staphylococcus (MRS) is being identified as a cause of skin infections in dogs. The MRS may belong to the species Staphylococcus aureus (MRSA), Staphylococcus pseudintermedius (MRSP), Staphylococcus intermedius (MRSI), Staphylococcus schleiferi (MRSS) or rarely Staphylococcus lugdunensis or Staphylococcus delphini.

No member of the beta lactam family of antibiotics will be effective when a MRS is identified. If the laboratory reports methicillin (oxacillin) resistance but susceptible to some other members of the beta lactam family of antibiotics you should contact the laboratory to clarify- either the report on the methicillin resistance is incorrect or the reported susceptibility to the other beta lactam antibiotic is incorrect. Complicating the treatment of MRS is that these bacteria are frequently multi-drug resistant (MDR). In a study by Bemis, et al21 it was found that more than 90% of the MRSP were MDR. MDR was defined as being resistant to 2+ antimicrobial drug classes. The cause of the increased frequency of MRSP has not been clearly established but one of the many risk factors for MRSA and MDR staphylococcus is the administration of fluoroquinolones. Reducing the administration of antibiotics and particularly fluoroquinolones and 3rd generation cephalosporins may help prevent persistent carriage of MRSA in humans.22,23 In study, the hospital recognized that MRSA outbreaks was correlated to the overuse of third-generation cephalosporins for prolonged periods24. Additional information about the administration of 3rd generation cephalosporins or fluoroquinolones is discussed below.

The purpose of this lecture is to help stem the rising incidence of MRS in our cases of canine pyoderma.

Bacterial culture and susceptibility (c/s) testing should be performed in cases of poorly responsive (NOT recurrent) SBF. If a deep pyoderma has exclusively rods on cytology, has been treated with antibiotics recently or the dog is systemically ill then a culture and susceptibility test should be performed on the first visit. If a c/s is submitted, the MIC (broth microdilution technique) method should be used to determine the susceptibility rather than the disc diffusion method (Kirby-Bauer). The disc-diffusion susceptibility test (DDST) is semiquantitative in that the drug concentration achieved in the agar surrounding the disc can be roughly correlated with the concentration achieved in the patient’s serum. It will only report the organism’s susceptibility (susceptible, intermediate or resistant) based on an approximation of the effect of an antibiotic on bacterial growth on a solid medium. Tube dilution (MIC) is quantitative, not only reporting SIR but also the amount of drug necessary to inhibit microbial growth. The MIC is reported as the amount of antibiotic (in µmg/ml) necessary to inhibit the growth of the tested bacteria (the lowest concentration in the tube that is clear). This allows a clinician to not only decide susceptible or resistant but also the proper dosage and frequency of administration of the antibiotic. Note that if the MIC for the bacterial isolate falls in the susceptible category, there is a greater likelihood of successful treatment (cure) than if the isolate were classified as resistant. It does not assure success; drug failure is still possible owing to other drug or patient factors such as the location of the infection and the immunologic status of the host. The intermediate category is not intended to mean “moderately susceptible.” If the MIC value is in the intermediate category, therapy with this drug at the usual standard dosage is discouraged because there is a good likelihood that drug concentrations are inadequate for a cure. However, successful therapy is possible when doses higher than the label dose is used or if the drug is concentrated in the affected organ (eg urine) or is used topically. If the MIC is in the resistant category, treatment failure is more likely because of resistance mechanisms or inadequate drug concentrations in the patient. However, a patient with a competent immune system may sometimes eradicate an infection even when the isolate is resistant to the drug based on the MIC. Lastly not only does the MIC method indicate susceptibility, but it also implies the relative risk of emerging resistance and thus the need for a high dose.

In regards to bacterial skin cultures- to interpret and use a susceptibility test based on MIC requires the following information:

1. First confirm that the organism is an expected pathogen from the skin
   a. *Staphylococcus pseudintermedius*
   b. *Staphylococcus intermedius*
   c. *Staphylococcus delphini*
   d. *Staphylococcus schleiferi coagulans*
   e. *Staphylococcus schleiferi schleiferi*
   f. *Staphylococcus lugdunensis*
   g. *Staphylococcus aureus*

2. MIC of the antibiotic in relationship to the organism. This is reported on the culture results.

3. The breakpoint is the highest plasma concentration of the drug that can safely be achieved in the patient. If the MIC exceeds the breakpoint this means that in order to inhibit visible growth in the test tube, the drug concentration exceeds what can safely be obtained in the patient’s plasma. The breakpoints for each antibiotic should be available from your laboratory. Currently MSU’s DCPAH website has a breakpoint chart available go to https://www.animalhealth.msu.edu/Sections/Bacteriology/WEBCD.BACT.REF.011.pdf

4. You then look at the culture results and list all the antibiotics that are reported as ≤ X where X is the listed MIC for each antibiotic

5. For the next step you need to be aware that within a population of susceptible bacteria there is a mixture of strains (heterogeneity). Some of the strains are very sensitive to a given antibiotic while others are less susceptible. The less susceptible ones would be the ones w/the MIC closer to the breakpoint (resistant MIC level). From the list you made in step 3 you need to rank the antibiotic based on which have the most susceptible bacteria. You do this by calculating the efficacy ratio. This number is the breakpoint of the antibiotic divided by the MIC of the bacteria. The higher the number the more susceptible the bacteria is to that antibiotic.

6. You will need to take the list from step 4 and decide which antibiotic fulfills your needs based on
   a. High efficacy ratio
   b. Ability to penetrate the infected tissue
   c. Side effects of the drug
   d. Ease of administration (consider both route and frequency required)
   e. Cost of the medication

7. If there are no antibiotics w/≤ X or the ones that do are either too toxic or too expensive you should then list the remaining antibiotics that are reported as susceptible. From this list you need to calculate the efficacy ratio. Remember this number is the breakpoint of the antibiotic divided by the MIC of the bacteria. The higher the number the more susceptible the bacteria is to that antibiotic. For example you have a staph that has a MIC of 1 umg/ml to enrofloxacin and has a MIC of 4 umg/ml to cephalexin. Which antibiotic is the population of bacteria most susceptible to? To determine this you take the breakpoint of enrofloxacin (4) and divide it by the MIC (1) and the efficacy ratio is 4. Doing the same to cephalexin you get (32/4) 8. Remember the higher the number the more susceptible the bacteria is to that antibiotic. So cephalexin would have the highest number of susceptible bacteria

8. With this list of antibiotics and their efficacy ratio, apply the criteria listed in step 5 to determine the most appropriate antibiotic

In humans the MRS organism is *Staphylococcus aureus*. In animals the staphylococcus responsible for infection usually belongs to the staphylococcus intermedius group (S. intermedius, S. pseudintermedius, and Staphylococcus delphini). Currently the protocol for identifying MRSA in vitro is to use cefoxitin as the surrogate. The problem is that certain strains of methicillin-resistant S pseudintermedius (any in the SIG?) may be falsely identified as methicillin susceptible, while truly being resistant, if the laboratory uses cefoxitin susceptibility as the indicator. This is because cefoxitin may not induce the mecA gene as reliably in S pseudintermedius as it does in *Staphylococcus aureus*. It is important that laboratories know this and use oxacillin susceptibility testing for identifying MR *S pseudintermedius* isolates (all SIG?) instead. In order to avoid mislabeling MRSP as susceptible the laboratory needs to know that the breakpoint for *S pseudintermedius* has been lowered from the previous level of 2.0 umg/ml down to 0.25 umg/ml. Why is this clinically important? If you are using a human laboratory, or a local laboratory, they may not be aware of this difference in testing between *S. aureus* and *S pseudintermedius*. Because of this, the author strongly recommends using a veterinary laboratory that uses Clinical and Laboratory Standards Institute (CLSI) guidelines.
Recently the effectiveness of clindamycin against MRSA has been questioned25. There are 2 genes, msrA and the erm gene family that are responsible for S. aureus’ resistance to macrolides (eg erythromycin). The msrA gene accounts for the resistance to beta lactams and macrolides, while the erm gene codes for macrolides and lincosamides (lincomycin and clindamycin) resistance. The erm gene expresses macrolide resistance constitutively while the clindamycin resistance can be either constitutive or inducible. Constitutive expression means that this gene will be active in the bacteria from the onset and the culture will report resistance to erythromycin and clindamycin. However if the erm gene is an inducible gene then only if there is a mutation in the erm genes will resistance occur. These mutations occur at a rate of about one in every 10^6 bacteria. Because most bacterial infections have bacterial populations that are in the range of 10^7-10^10 these mutations readily occur, resulting in constitutive resistance. This leads to resistance to clindamycin while on treatment. As the susceptibility pattern to clindamycin of MRSA isolates (or MSSA) possessing only the msrA gene (truly resistant to erythromycin and susceptible to clindamycin) and those that also have the inducible erm gene (truly resistant erythromycin and falsely reported as susceptible to clindamycin) are the same, it is important to distinguish between these phenotypes. Unfortunately no commercial lab is currently doing any additional testing to identify the erm resistance gene. So in the mean time resistance to erythromycin may be used as a clue to the presence of this inducible gene. It is best to avoid clindamycin in any MRSA infection if the organisms is reported to be resistant to erythromycin. Note this inducible gene has rarely been reported in MRSP26.

In the tetracycline family there is a gene (tet m) that is responsible for bacterial resistance to tetracycline, doxycycline and minocycline. However there is an inducible gene tet (k) that is responsible for resistance to tetracycline and inducible resistance to doxycycline but the bacteria are not resistant to minocycline. Because of this, minocycline should be tested separately from tetracycline/doxycycline27,28.

Systemic therapy for canine pyoderma is becoming more problematic because of the increasing incidence of methicillin resistant Staphylococcus. 29,30,31,32 To help address this problem topical therapy, either as a monotherapy or as part of polypharmacy, has become an essential component of managing SPF. Topical therapy may decrease the length of time administering, or eliminate the need for, systemic antibiotics. Since dogs with SBF frequently have atopic dermatitis, bathing will remove problematic allergens, in addition to bacteria from the skin. The limitations of using topical therapy include time constraints of the owner and, if treating a large area, possibly cost. Shampoo ingredients that are effective for treating bacterial pyoderma include chlorhexidine, benzoyl peroxide, ethyl lactate, tricosan and boric acid/acetic acid. In 2 different studies, chlorhexidine was the most effective ingredient.33,34

Silver sulfadiazine has traditionally been used for to treat gram negative bacteria, especially Pseudomonas.35 However it is also effective against some gram-positive bacteria including Staphylococcus aureus.

When treating a dog with a SBF, an antibiotic should be administered for at least 21 days, or 14 days past YOUR clinical examination that has determined the infection has resolved, whichever is LONGER. For dogs with deep pyoderma, treat for at least 6 weeks or 21 days beyond clinical resolution, whichever is longer. In cases of SBF don’t use glucocorticoids (GC) when the pruritis is only at the lesions or when the pruritis is only mild at the nonlesional areas. If a dog with a SBF has intense pruritis at nonlesional

33 Loeffler A, Cobb MA, Bond R Comparison of a chlorhexidine and a benzoyl peroxide shampoo as sole treatment in canine superficial pyoderma The Veterinary Record 2012;170:26 675
36 Drug insert-silvadene: http://www.drugs.com/pro/silvadene.html
areas then a tapering 21 days course of prednisone may be dispensed. Using GC in the presence of a pruritic pyoderma makes interpretation of response to therapy impossible (was it the steroid or treating the infection that resolved the pruritus?). It also makes it more difficult to resolve the infection. NEVER use GC in cases of deep pyoderma!!

Before discussing systemic antibiotics for bacterial pyoderma, the author needs to make a few comments about cefpodoxime and cefovecin. Cefpodoxime is an oral 3rd generation cephalosporin effective for most of the staphylococcus infections that occur in dogs. This once a day antibiotic is useful in cases where the owner has difficulty administering medication. However recently, cephalaxin has become available as a chewable tablet (Rilexine® Virbac) that should help make administration of cephalaxin much easier. The once daily administration and the formulation in a pill rather than a capsule may make it easier for some owners to medicate their dog. Another instance where it may be of use is during a food trial. During this trial it is best, if possible, to avoid gelatin (animal protein) that is present in capsules. Using cefpodoxime tablets would solve this problem. The author also has an impression that there are fewer intestinal disturbances using cefpodoxime versus cephalaxin. However, consider when dispensing cefpodoxime there are some staphylococcus infections that will be resistant to cefpodoxime but susceptible to cephalaxin37. Also the stated higher compliance rate of once daily medication vs twice daily may not be true. Adams et al reported that in their study there was no difference in compliance with once daily versus twice daily dosing38. Lastly there are numerous studies showing that once daily cephalaxin at 30-40 mg/kg is as effective as splitting this dose and administering q 12 hours.39,40,41,42,43,44,45 HOWEVER these were not peer reviewed studies so this is NOT my recommendation. However these studies do suggest that missing 1 dose of cephalaxin is not catastrophic.

In addition remember missing one dose of a once daily pill would be the same as missing TWO doses of a twice daily pill. See comments about 3rd generation cephalosporins use below.

Cefovecin is a parenterally administered 3rd generation cephalosporin that has tremendous value when used properly (selectively). Cefovecin may persist in the body for up to 5 weeks; therefore, adverse event monitoring should be carried out for a similar amount of time. (note USA insert states reactions may require prolonged treatment due to the prolonged systemic drug clearance (65 days ). The drug insert from the New Zealand product states “Prudent Use: It is prudent to reserve third generation cephalosporins for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials including first generation cephalosporins. Use of the product should be based on susceptibility testing and take into account official, and local, antimicrobial policies. Indiscriminate use of cefovecin could contribute to the development of antibiotic resistance.”

This author believes that this drug should be reserved for cases where the owner is unable to orally medicate the dog or cat or the animal can’t tolerate oral antibiotics. The concern about using this medication is that after the first injection therapeutic drug concentrations (above MIC) are only maintained for 7-14 days, depending on the infectious agent, while tissue levels persist for up to 65 days46. The question is whether this prolonged subtherapeutic blood (tissue?) level will encourage the incidence of methicillin resistant staphylococcus. Will adverse reactions require prolonged treatment due to the prolonged systemic drug clearance? What are the long-term effects on injection sites, especially in cats? How clinically significant is the in vitro finding that cefovecin increases free concentrations of carprofen, furosemide, doxycycline, and ketoconazole. Will drugs with a high degree of protein-binding (e.g. cardiac, anticonvulsant, and behavioral medications) compete enough with cefovecin-binding to create adverse reactions. Most of these questions have not been answered, even by the company.

37 Rankin SC, O’Shea K, Morris DO: Susceptibility of companion animal isolates of Staphylococcus schleiferi to cephalothin and cepfodoxime. Vet Derm 17:3:214
40 Cadot P., Salomon, C., Carlotti, DN.:Treatment Of Superficial Pyoderma In Dogs: Cephalexin In A Single Dose Versus Marbofloxacinet. Proceedings 26th World Veterinary Congress WVVA, Lyon, France, September 1999
46 Pfizer drug insert – prescribing information for Convenia
In the BSAVA Guide to the Use of Veterinary Medicines, it discusses the prudent use of antimicrobial agents. In regards to 3rd generation cephalosporins and also for any fluoroquinolones (FQ) it states “that in all species fluoroquinolones and third- and fourth-generation cephalosporins should be used judiciously and never considered as first-choice options”.

The Europeans are also concerned about 3rd generation cephalosporin use and FQ use. The European Medicines Agency states (EMEA/CVMP/215997/2006) “Following advice given by the CVMP Scientific Advisory Group on Antimicrobials (SAGAM), the CVMP agreed the following statements should be included in section 4.5 of the SPC (special precautions for use) “It is prudent to reserve third generation cephalosporins for the treatment of clinical conditions, which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials or first generation cephalosporins.” and “Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies”.

The Swedish veterinary medical society published guidelines in 2009 for the use of antibiotics in the treatment of dogs and cats. In this guideline it is stated very clearly that third generation cephalosporins should only be used to treat infections where there are no other suitable options. It goes on to state that injections with long-acting antibiotics should normally be used to treat a pyoderma. Specifically in the guidelines it states that cefovecin should only be used if the treatment is “of the utmost importance” for the animal AND administration of other medications is not possible.

The Norwegian Antibiotics Policy states that “Antimicrobial drugs considered critically important for human health by the WHO: Fluoroquinolones, macrolides, glycopeptides and 3rd and 4th generation cephalosporins, should always be considered last resort and never be prescribed unless c/s dictates that there are no other available drugs that can be used to treat the infection. They go on to state “Long acting drugs or slow release formulations should be used very cautiously as the documentation is lacking with regards to the impact these drugs may represent with regards to resistance development in the normal flora.”

The concern with using FQ is that, according to information from the CDC website, “none of the fluoroquinolones are FDA-approved for treatment of MRSA infections. A major limitation of fluoroquinolones is that resistant mutants can be selected with relative ease, leading to relapse and treatment failure”. MRSA strains are especially adept at developing fluoroquinolone resistance, and such resistance is already found among MRSA isolated from patients with CA-MRSA infections. In addition it has been reported that there is a significant association between total fluoroquinolone use within human hospitals and percentage of S. aureus isolates that were MRSA and between total fluoroquinolone use in the community and percentage of E. coli isolates that were fluoroquinolone-resistant E. coli. It has been noted that there has been an increase in the number of ESBL E. coli and Salmonella spp. in the absence of prior exposure to the cephalosporins, suggesting potential coselection and co-resistance. Lastly, even after selection pressure is removed (stopped using the FQ), fluoroquinolone resistance persists.

Additional concern about both FQ and 3rd generation cephalosporins is that they are both independent risk factors for development extended spectrum beta-lactamase (ESBL) producing bacterial infections. Extended-spectrum beta-lactamases (ESBLs) are beta-lactamase-producing bacteria in nonhospitalized patients. European journal of clinical microbiology & infectious diseases 23(3), 163-167.
lactamases found in *Enterobacteriaceae* (E. coli, K. pneumoniae, etc) and are a concern in human medicine because they cause serious infections in humans. These bacteria are frequently multi-drug resistant, not only to beta lactam antibiotics, but also to non beta lactam antibiotics such as aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, and sulfamethoxazole-trimethoprim. This wide ranging resistance greatly limits effective treatment options. The genes encoding this resistance are mediated by plasmids and/or mobile elements which allows horizontal transfer between the same and different species of *Enterobacteriaceae* making wide spread dissemination a concern.\(^\text{58}\) In contrast to FQ and 3^{rd} generation cephalosporins, first generation cephalosporins have not been reported to be a risk factor for such resistance.\(^\text{56}\)

A consensus statement has been released with the purpose of guiding practitioners in the diagnosis, treatment and prevention of superficial bacterial folliculitis (SPF)\(^\text{59}\). These guidelines, like the previous guidelines published concerning antibiotic use for treating urinary tract infections\(^\text{60}\), are the result of a committee consisting of veterinary internists, pharmacologists, microbiologists and dermatologists. In this article it is stated that “there is concern among some members of this panel about the potential selective effects of third generation cephalosporins (cefodoxime and cefovecin) on the Gram-negative microbiota, due to their broader spectrum of activity compared with first generation cephalosporins”. The key points are:

1. Identify and treat the underlying cause for SPF;
2. Perform skin scrapings to identify demodex mites;
3. Perform cytology to confirm a bacterial component;
4. If possible use disinfectants and/or topical antimicrobials as the sole treatment. If this is not possible, at least use topical therapy to shorten the length of time that systemic antibiotics need to be used;
5. Empirical therapy can be done in non recurrent cases or recurrent cases that have successfully responded to previous treatment. You should select a drug from the list of first tier medications. This list includes (the author will prescribe the drugs in bold):
   a. Clindamycin- Antirobe® 5-10 mg/# sid \(^\text{61},62,63,64,65\)
   b. First generation cephalosporin
   c. Cephalexin 10-15 mg/# bid-tid
   d. Cefadroxil – 10 mg/# bid
   e. Amoxicillin/clavulanic acid – Clavamox® 10 mg/# bid
   f. Potentiated sulphonamides
   g. Trimethoprim/sulphonamide- Tribrissen® 15 mg/# bid
   h. Sulfadimethoxine and ormetoprim- Primor® 25 mg/# sid on day 1 then 12.5 mg/# sid
   i. Erythromycin
   j. Lincomycin

6. In cases which fail to respond to appropriate treatment (dose and frequency) using a first tier antibiotic, a bacterial culture should be performed. When selecting an antibiotic based on a culture result, a sensitive second tier antibiotic

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should ONLY be used if the organism is resistant to all first tier antibiotics OR the animal can’t tolerate any of the first tier drugs OR the owner is unable to administer them. The second tier antibiotics include:

a. Any fluoroquinolone (FQ)
   i. Please note- when appropriate, a veterinary FQ should be administered rather than ciprofloxacin. This recommendation is based on a study that revealed that there is a very large variation in absorption of ciprofloxacin. In this study it was reported that in order to get appropriate blood levels you would need to dose ciprofloxacin at 12–52 mg/kg. This is for highly susceptible (low MIC) organisms, not the ones with higher MICs!

b. Chloramphenicol
c. Rifampin
d. Doxycycline/minocycline

7. 3rd tier antibiotics should never be used without consultation with a specialist – these are vancomycin and linezolid.

Note in regards to 3rd generation cephalosporins (cefovecin, cefpodoxime). In this report they state there is insufficient evidence for this working group to reach consensus on categorization of these agents as first or second tier drugs (see text under ‘Systemic antimicrobial therapy’ and concerns about selection of ESBL-producing Enterobacteriaceae). Author’s comment- since there is a disagreement on the use of these drugs, why not reserve 3rd generation cephalosporins for cases where first generation would not be appropriate.

Recently Dr Scott Weese wrote an editorial for Clinicians Brief, (CB) He states that “this journal (CB) like Equine Veterinary Journal will avoid articles that recommend extra-label use of fluoroquinolones and extended-spectrum beta-lactam antimicrobials (eg, third- or fourth-generation cephalosporins). Consideration for their use will occur if there is specific mention of the relevant issues, and evidence supporting that recommendation is provided.”

This author wants to remind the readers that cefovecin is ONLY labeled for the treatment of canine skin infections (secondary superficial pyoderma, abscesses, and wounds) caused by susceptible strains of Staphylococcus intermedius and Streptococcus canis (Group G). Cefpodoxime is ONLY indicated for dogs with skin infections (wounds and abscesses) caused by susceptible strains of Staphylococcus intermedius, Staphylococcus aureus, Streptococcus canis (Group G, β-hemolytic), Escherchis coli, Pasteurella multocida, and Proteus mirabilis. So as stated above other usage should be avoided.

Lastly, ACVIM published a consensus statement on antimicrobial use in animals and they state “fluoroquinolones and later generation cephalosporins possess activity against a wide range of bacteria and potential far-reaching effects on the microbiota. While limiting use of classes such as the 3rd generation cephalosporins and fluoroquinolones is widely accepted and consistent with principles of antimicrobial stewardship…” Again this reiterates the recommendation of restricting the use of these antibiotics.

Bottom line – we should be very selective when dispensing any antibiotic but especially fluoroquinolones or any third- and fourth-generation cephalosporins in the treatment of canine bacterial pyoderma.

However to be clear - ALL antibiotics have consequences. This was demonstrated in a report of 173 dogs presented to a dermatology referral practice for treatment of a bacterial pyoderma. The study evaluated the impact of routine antimicrobial therapy on emergence or resolution of resistant bacteria in a group of 173 dogs presented to a dermatology referral practice for treatment of a bacterial pyoderma. Additionally it evaluated the prevalence of MRSP colonization after successful treatment of their bacterial pyoderma. In this study skin, nasal and rectal swabs for bacterial culture were collected at the time of referral and after clinical resolution of the pyoderma. Of dogs that initially had an MRSP pyoderma, 26 of 42 (61.9%) were colonized at one or more sites at

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67 Weese JS Prudent Antimicrobial Use in an Antimicrobial-Resistant World. Clinician’s Brief 2015: June; 10-11

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follow-up, even though the pyoderma had resolved. Of the 60 dogs with a non-MRSP pyoderma on initial presentation, 23 (38.3%) were colonized with MRSP at one or more sites after clinical resolution of the pyoderma.

It is apparent from this information that the older mindset “I wasn’t sure what to do so I put him on antibiotics since they won’t hurt him” needs to be changed. Even though using antibiotics may not harm that individual animal at that time, we are now, and may continue, to suffer the consequences with the spread of resistant bacteria (both human and veterinary). Hopefully we can disrupt this disturbing trend with good stewardship of the use of antibiotics.
Pemphigus

In pemphigus, the immune system is directed to inappropriately attack the desmosomes. Desmosomes are spot-like sites of intercellular contact and attachment between keratinocytes.

Pemphigus foliaceus (PF) is the most common form of pemphigus and is probably the most frequently diagnosed autoimmune skin disease (AISD) affecting cats and dogs. Other forms of pemphigus that will be seen in practice include pemphigus erythematosus (PE) and panepidermal pemphigus (PPP). In general, PF is a disease of young to middle-aged animals with a mean age of onset of 4 years old. Sixty-five percent of the dogs have the disease before 5 years of age. PF has been reported in numerous breeds with Chow Chows and Akitas being at increasing risk in the author’s practice. There is no gender predilection in dogs.

In the author’s experience, even though there are three forms of PF reported in the literature—spontaneous pemphigus, drug-related (both drug induced and drug triggered), and a form that is associated with chronic skin disease, it is rare to have cases in which the dog has had chronic skin disease. In fact, there is no evidence to support that claim. Cases that occur spontaneously are by far the most common.

Historically, the owner may report that the lesions wax and wane or are progressive. The progression of the disease may be slow, especially cases with only facial involvement, or the dog may develop acute eruptions (most commonly associated with generalized disease). With the generalized form, the dogs frequently will be febrile, may have limb edema and have constitutional signs. Pruritus with any form varies from non-existent to moderately intense.

There are three primary distribution patterns of PF: facial (most common) form which involves the bridge of the nose, nasal planum, periorbitally, pinnae (especially in cats); a footpad form (cats may present only with paronychia) and a generalized form where lesions usually begin on the face and then spread. Note that there is a subset of dogs that have generalized disease from the onset.

The lesions progress from an erythematous macule → pustule → collarettes → erosions → yellow brown crusts. Because there is involvement of the hair follicles, multi-focal to diffuse alopecia is frequently present. The primary lesions of PF are large non-follicular pustules (there are also follicular pustules present) especially involving the bridge of the nose, footpads, nasal planum or pinnae (cats may have lesions around the nipples). This is in contrast to pustules associated with a bacterial pyoderma in which the pustules are follicularly oriented. The pustules that are present in a bacterial pyoderma usually involve the ventral abdomen and/or trunk and are much smaller than those seen with PF. In cats and dogs with PF, secondary lesions are more commonly seen than the pustules. These lesions include epidermal collarettes, yellow brown crusts and erosions. These animals may be systemically ill, have distal limb edema, fever, lethargy and/or lymphadenopathy.

Differential diagnosis would include any pustular, crusting and scaling disease such as: pemphigus erythematosus; zinc responsive dermatosis (especially with foot pad involvement); metabolic epidermal necrosis (especially with foot pad involvement); bacterial and fungal (dermatophytosis) infections; demodicosis, DLE (facial/nasal form); erythema multiforme; mycosis fungoides; Leishmaniasis; and sebaceous adenitis.

Diagnosis

A cytologic prep of a pustule or crust should be performed. Microscopic findings would include acantholytic keratinocytes, either individually or in clusters, surrounded by NON-degenerative neutrophils and/or eosinophils—bacteria should not be seen.

Histopathology is the only definitive means to diagnose pemphigus. An intact pustule (or if none are present, a crusty lesion) should be biopsied. Infectious diseases that produce proteases, such as a bacterial pyoderma or a dermatophyte infection (Trichophyton mentagrophytes), can breakdown the intracellular glycoproteins (desmoglein) leading to acantholysis. Because these infectious organisms share the ability to breakdown desmoglein, it can be difficult to distinguish between PF and other infectious diseases.

The diagnosis of ANY skin disease is based on obtaining a detailed history, evaluating clinical findings (identification of primary lesions, distribution of lesions), laboratory testing and therapeutic trials. For autoimmune skin diseases (AISD) the most beneficial diagnostic tool is histopathologic evaluation.

diseases mimic PF histologically, you should request special stains for both bacteria (gram stain) and fungi (GMS, PAS) anytime a there is a histopathologic diagnosis of PF.

**Prognosis**

PF may be drug related, either drug-induced or drug-triggered\(^{75, 76}\). The drug-induced form PF is caused by a drug and upon removal of the drug, sometimes with a short course of immunosuppressive treatment, the disease resolves. Drug-triggered PF occurs when a drug stimulates a genetically predisposed individual to develop PF. Typically, this form of PF must be managed long term, similar to idiopathic PF. Currently there is no way to identify which cases of drug related PF are drug induced and which ones are drug triggered. In fact there is no test that can be used to predict how well a case of PF will respond to treatment.

A study at NCSU\(^{77}\) revealed that 6 of 51 dogs (11.7%) with PF were weaned off all medication and stayed in remission for >1 year. Recognizing that PF is a sunlight aggravated disease, it was interesting the dogs in this study were from areas (NC or Sweden) with high UV light exposure. In this report the dogs took 1.5–5 months of therapy before the disease was in remission. The drug(s) were then slowly tapered and then all therapy was stopped. The total duration of immunosuppressive therapy varied between 3 and 22 months. These dogs stayed in remission for the entire follow up period (1.5–6 years after treatment). Supporting this finding is a study from the University of Pennsylvania that reported that 10% of their cases went into long-term remission after weaning off medication.\(^{78}\)

This study performed at the University of Pennsylvania suggests that dogs with PF survived longer when given antibiotics (usually cephalaxin) in addition to their immunosuppressive regimen. This is in contrast to the author’s clinical observation that if dogs with PF do develop a concurrent pyoderma it only occurs AFTER being placed on immunosuppressive therapy. Supporting the author’s observations is a study from CSU that reported that there was no difference in survival when antibiotics were part of the initial treatment.\(^{79}\)

In the study from University of Pennsylvania the survival rate was approximately 40% with 92% of the deaths occurring by 1 year. Other researchers have reported having a long-term survival rate of approximately 70%.

Cats may have a better prognosis than dogs with this disease. In the same report from the University of Pennsylvania, only 4/44 cats treated died (from their disease or therapy) during the study period. In the author’s practice, survival at 1 year also exceeds 90%. In addition, a significant number of the cats are eventually able to have all medications discontinued without suffering a subsequent relapse.

**Treatment**

Managing any AISD takes frequent rechecks and alertness to complications associated with immunosuppressive therapy such as demodicosis, dermatophytosis and bacterial pyoderma. Interestingly, the author has rarely seen a dog with PF that had a secondary pyoderma at initial presentation. It is more common to develop after beginning immunosuppressive therapy. If a patient was controlled and then has a relapse or if the patient has been improving and suddenly worsens, there are 2 possibilities. The PF (which does wax/wane) is flaring up OR that the dog developed a secondary infection due to immunosuppression. If the new lesions are folliculocentric you must also rule the big 3 folliculocentric infections - bacteria, demodex and dermatophyte. Skin scrapings, Wood’s light examination (screening test) and impression smears are the minimum data based that should be performed when a dog is presented with these lesions. Whether or not you need to do a fungal culture at this time depends on the how frequently you see dermatophytosis in your practice and what is seen on cytology (acantholytic keratinocytes, cocci, demodex mites). If dermatophytosis is commonly seen in your practice then a fungal culture should be performed. Otherwise a fungal culture and a repeat skin biopsy can be considered second tier tests to be performed if the case doesn’t respond to appropriate therapy (eg antibiotics)

In addition to the treatment options listed below, shampoo therapy should be included for symptomatic treatment of the crusty dermatitis. Pending biopsy results, if intracellular cocci are seen on cytology the author will dispense cephalaxin (10-15 mg/# bid-tid),


unless there is a suspicion that it is a case of cephalaxin induced PF. If only extra cellular cocci are seen, then topical shampoo therapy with an antiseptic (eg chlorhexidine, benzoyl peroxide, etc)

Treatment must be individualized for each patient since there is no “best” treatment that works in all PF patients. This is why monitoring the progress of the disease closely by PHYSICALLY examine the dog or cat is critical for successful management of PF. It is especially important to recheck the patient prior to any adjustment in medication. When devising a treatment plan, be sure to consider the severity of the disease so that the treatment side effects are not worse than the disease itself.

There may be regional differences in how aggressively PF needs to be treated. Some of this may be due to the differences in the gene pools of the patients. But since PF is a sunlight aggravated disease, it also may be related to the differences in sun exposure. Regardless of the locale, sun avoidance should be part of the treatment for PF.

Because diet has been implicated as a cause of PF (endemic) in humans, the author will review the dietary history and consider dietary modification if the initial response to therapy is poor. The ingredients implicated in human endemic PF contain thiols (eg garlic, onion), isothiocyanates (mustard, horseradish), phenols (food additives) and/or tannins (tea, bananas, and apples).

Vitamin E (400-800 IU bid) and essential fatty acids may be used as part of the treatment since these nutrients have anti-inflammatory properties and anti-oxidant activities.

For mild or localized disease a tetracycline with niacinamide may be used. This is because tetracycline family and niacinamide (T/N) have a variety of anti-inflammatory & immunomodulating properties the combination has been used in treating a variety of immune mediated skin diseases, such as discoid lupus erythematosus, vesicular cutaneous lupus erythematosus (idiopathic ulcerative dermatosis of collies and Shelties), lupoid onychodystrophy, pemphigus erythematosus, German Shepherd Dog metatarsal fistulae, sterile panniculitis, sterile periadnexal granulomatous dermatitis (idiopathic sterile granuloma-pyogranuloma syndrome), vasculitis, dermatomyositis and cutaneous histiocytosis. The author may use this combination for any of the previous mentioned diseases if the disease is relatively mild. If any of these diseases fail to respond well to immunosuppressive therapy, T/N may also be added to the therapy in dogs.

Traditionally tetracycline was the drug used from the tetracycline family but when it became unavailable then doxycycline was used. But with the increasing occurrence of meticillin resistant staphylococcus infections, using antibiotics for immunomodulating properties has become a concern, this is especially true for doxycycline because it is considered a second line antibiotic in the treatment of bacterial pyoderma in the dog. Studies in humans have failed to show any evidence that subantimicrobial doxycycline treatment (20 mg bid for 9 months) exerted an effect on the composition, or doxycycline resistance level, of either the fecal or the vaginal microflora. Additional studies in humans using 40 mg for 16 weeks revealed that a subantimicrobial doxycycline dose (40 mg) had a minor ecological effect on the oropharyngeal and intestinal microflora. A third study in humans revealed that long-term oral administration of 40 mg of doxycycline once daily results in no antimicrobial resistance. A study was performed on beagle dogs that revealed that doxycycline at 2 mg/kg daily appeared to be an appropriate subantimicrobial regimen for dogs with periodontitis. It appears as though this dosage may be suitable for long-term treatment of gelatinolytic inflammatory diseases. Whether that is true for other inflammatory or immune mediated diseases has not been studied. Based on these 4 studies, the author’s concern about antimicrobial resistance and the lack of any evidence based studies supporting any other dose, the author now will use doxycycline at 2 mg/kg sid. On the limited number of cases that have been treated it appears as though this dose is effective.

The dosage niacinamide in dogs < 10 kg is 250 mg of each, q 8 hours. For dogs >10kg - 500 mg of niacinamide q 8 hours is administered. If there is a clinical response, which may take a few months, the frequency of administration may be slowly

80 Olivry T. Canine pemphigus foliaceus: an update on pathogenesis and therapy In: Clinical Programme Proceedings of the Fifth World Congress 222-227
decreased (q 6 months or so) Side effects are rare but they include include vomiting, anorexia, lethargy, diarrhea and elevated liver enzymes.

Glucocorticoids (GC) are the mainstay of therapy for AISD. They may be applied topically or administered systemically depending on severity of the disease and the amount of the body involved. Since some cats can’t metabolize inactive prednisone to the active form, prednisolone, ONLY PREDNISOLONE should be used in cats. In dogs either prednisone or prednisolone may be used. The author has seen cases of feline PF, which were well controlled on prednisolone, but when prednisone was dispensed relapsed, only to go back into remission once the cat was placed back on prednisolone—all at the exact SAME dosage and frequency.

The most potent topical GC (Veterinary product) is a product containing flucinolone acetonide (Synotic®). For localized disease the author will apply this product bid until clinical remission (not to exceed 21 days) and then tapered slowly over the next few months. Be sure to have the owners wear gloves when applying this product. If this treatment is unsuccessful the one of the following systemic therapies will be instituted.

In dogs with more extensive disease or those that fail topical therapy, prednisone or prednisolone is administered at 1 mg/# bid for 4 days then ½ mg/# bid for another 10 days. The dog is rechecked every 14 days. If the disease is in remission, the dose is decreased 25% at each recheck examination. The author defines “remission” as the absence of any active lesions (no pustules and any crusts that are present are easily removed with the underlying epidermis appearing pink rather than erosive). DON’T TAPER THE DOSE TOO QUICKLY. The goal is to maintain the dog on 0.25 mg/# or less every other day of prednisone/prednisolone. If this is not achievable, then azathioprine is added to the therapy (see below). Some dermatologist will use the combination therapy from the onset, but because at least 75% of the dogs in the author’s practice can be maintained on just GC and there are additional risks and costs associated with this drug the author considers this a second tier therapy 79. Only if the dog fails to respond to GC, or can’t be managed with every other day administration, will the author add azathioprine to the therapy.

For cats, ONLY prednisolone is used and in fact only prednisolone is stocked in the author’s pharmacy—this is to avoid the inadvertent administration of prednisone to a cat. The dose for cats is 1 mg/# bid for 14 days. From that point forward the management of the cat with prednisolone is the same as the dog. If the disease is not controlled with prednisolone then CHLORAMBUCIL (see below) is added to the therapy NOT AZATHIOPRINE!!!

If an animal fails to respond to prednisolone other immunosuppressive agents (see below) will be added to the therapy. Animals on chronic GC, regardless of dose should have a CBC, serum chemistry profile, urinalysis every 6 months. The urinalysis is performed to identify proteinuria due to the steroid administration. There is no benefit to doing a urine culture if the dog or cat are asymptomatic since you will identify animals with asymptomatic bacteriuria which doesn’t need/should be treated. There is no evidence to the author’s knowledge that leaving a dog on cyclosporine or steroids with asymptomatic bacteriuria will lead to pyelonephritis. In a consensus statement, the ACVIM states that “treatment may not be necessary in animals that have no clinical signs of UTI and no evidence of UTI based on examination of urine sediment.” In humans they don’t treat asymptomatic bacteriuria except in pregnant women or type 1 diabetic patients or if undergoing a urologic procedures in which mucosal bleeding is anticipated.

In humans no recommendation can be made for screening for or treatment of asymptomatic bacteriuria in renal transplant or other solid organ transplant recipients.

Azathioprine (AZA) is an antimetabolite that is a competitive inhibitor of purine. Purine is necessary for DNA formation, so in the presence of AZA, defective DNA is formed preventing cell replication. It has a lag phase of four to six weeks before it reaches its full effectiveness. The drug is administered concurrently with GC. The initial dose of azathioprine is 1.0 mg/# sid. Once remission is achieved, and the dog is either off of GC, or the lowest dose of GC has been obtained, AZA is then tapered every 60-90 days. Usually the author will decrease the frequency, not the dose of azathioprine, first decreasing it to every other day and then if the disease is still in remission, to every 72 hours. A CBC, platelet count, serum chemistry profile are performed every 14 days for 2 months, then q 30 days for 2 months then q 3 months for as long as the dog is on azathioprine. Potential adverse effects include anemia, leukopenia, thrombocytopenia, hypersensitivity reactions (especially of the liver) and/or pancreatitis. AZA should not be used in cats—it may cause irreversible bone marrow suppression.

Chlorambucil (CAL) is used in cats and in dogs who failure to respond to azathioprine or can’t tolerate it. The protocol/precautions/monitoring for CAL is the same as w/AZA. The induction dose is 0.1-0.2 mg/KG/day. Note it too may have a 4-6 week lag effect.

Cyclosporine A (CSA), a calcineurin inhibitor, has been used orally at a dose of 5 mg/kg sid in cases of PF with poor results in dogs. Recently the author has used CSA at 5 mg/kg sid-bid with success either as monotherapy or as steroid sparing agent. There have been anecdotal reports of successful treatment of PF in cats (especially nail bed form) with CSA. Recently topical tacrolimus has been reported to be effective in the treatment of facial PF and PE. The author has limited experience with this product.

Sulfasalazine (SSZ) is a sulfa that has both anti-inflammatory and/or immunomodulatory properties due to its prostaglandin synthetase and leukotriene inhibition. In the past it has been used for the treatment of colitis but more recently it has been used for neutrophilic vasculitis. SSZ is metabolized by colonic bacteria to 5-aminosalicylic acid (5ASA) and sulfapyridine (SP). SP is well absorbed, metabolized in the liver, and excreted by the kidney while 5-ASA is much less well absorbed. Because SSZ is metabolized to aminosalicylic ("aspirin") this drug should be used cautiously in cats. The biggest concern with this medication is the possibility of developing irreversible keratoconjunctivitis sicca. This appears to be an idiosyncratic reaction that occurs more in smaller dogs but may occur in any dog. It is essential that you warn the owner that if the eyes become red or they notice an ocular discharge or squinting to contact you immediately so that you can do tear testing. Other side-effects associated with this drug include anemia, KCS and hepatotoxicity so a CBC, serum chemistry profile and Schirmer tear test are performed every 14 days for 2 months, then q 30 days for 2 months then q 3 months for as long as the dog is on SSZ. In cases of neutrophilic vasculitis that fail SSZ treatment w/dapsone may be effective, however, dapsone appears to be more toxic than SZA. The dose is 20-50 mg/kg tid (maximum 1 gm/dose), usually beginning with 20-30 mg/kg tid. Once the disease is in remission, the dose is slowly tapered.

Specific treatment approach- for mild cases of facial PF (or cases of pemphigus erythematosus), a topical glucocorticoid is used and/or T/N. For generalized forms, or in cases with severe facial and/or footpad involvement, prednisolone should be used as described above. As long as the disease is in remission at each recheck, the steroids are tapered as previously described. If the disease is not in remission at the first 14 day recheck or it can’t be kept in remission with steroids at a dose of <0.25 mg/# q 48 hrs, then either azathioprine (dogs) or chlorambucil (cats) is added to the treatment.

If the disease is not responding to the above treatment, CONFIRM that the diagnosis is correct (be sure to have ruled out dermatophytosis, demodicosis and bacterial pyoderma) then, changing to either dexamethasone or triamcinolone may be helpful. Use 0.05-0.1 mg/# bid of either drug, as the starting dose, and then taper as previously discussed.

As a “rescue” treatment for refractory cases of PF, high dose GC pulse therapy has been reported to be successful. Pulse therapy is followed by ½ mg/# bid of prednisolone and then taper as described previously. There are 2 protocols for pulse therapy:

1. 11 mg/kg of methylprednisolone sodium succinate (mixed w/250 ml of D5W) IV sid x 3-5 days 91
2. 10 mg/kg once daily for 3 days of prednisone ORALLY 92

Discoid lupus erythematosus (DLE)
The approach to diagnosing DLE is the same as PF- signalment, detailed history, physical findings, histopathology changes and response to therapy. In the dog, DLE is the 2nd most common autoimmune skin disease. The author has never recognized it in a cat. It has been suggested that there is no age predilection, but in the author’s experience it seems to be more common in young to middle aged-dog. Collies, Shelties, German shepherd dogs, Siberian huskies and Brittany spaniels are at risk breeds.

Clinical findings include depigmentation, erythema, erosions, crusts and alopecia. When the nasal planum is first affected there is loss of its normal cobblestone appearance and it develops a slate gray appearance. Depigmentation, erythema, erosions and crusts may occur over time. DLE usually begins on the nasal planum and may process to involve the bridge of the nose. It may also involve the lips, periorcular region, pinnae, and genitalia. Dogs affected with DLE are not clinically ill.

Differential diagnoses may include mucocutaneous pyoderma, pemphigus foliaceus, pemphigus vulgaris complex, cutaneous drug reaction, erythema multiformae, cutaneous lymphoma, uveodermato logic syndrome, SSC, solar dermatitis/collie nose and systemic fungal infections.93 94 95

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70. Griffies JD, Mendelsohn CL, Rosenkrantz WS et al Topical 0.1% tacrolimus for the treatment of discoid lupus erythematosus and pemphigus erythematosus in dogs, Veterinary Dermatology, 2002; 13: 211–229

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Mucocutaneous pyoderma (MCP) (the author feels a better name is “antibiotic responsive dermatitis” since bacteria are not seen histologically) is a crusting disease that may affect the lips, nasal planum (exclusively), the bridge of the nose, periorcular region, genitals or anus. Clinically it is indistinguishable from DLE. There is no identifiable cause for this disease and the diagnosis is based on the signalment (adult dog, most commonly in German Shepard Dogs (or mixes)), clinical appearance and distribution of the lesions and most importantly response to antibiotic therapy. In the past MCP was differentiated from DLE based on histopathologic findings. DLE was diagnosed when a lichenoid lymphocytic to lymphoplasmacytic interface dermatitis with hydropic degeneration and/or individual necrotic keratinocyte involving the basal cell layer, pigmented incontinence and a thickened basement membrane was present. Mucocutaneous pyoderma would be diagnosed histologically when a lichenoid plasmacytic to lymphoplasmacytic infiltration was present without an interface change and without basal cell damage. HOWEVER, this criterion has been called into question with a study that reported that histologically mucocutaneous pyoderma and DLE are indistinguishable! In that study, dogs were separated, based on histologic findings, into 3 groups, ones with lymphocytic lichenoid interface dermatitis with hydropic degeneration; ones with plasmacytic lichenoid dermatitis, and lastly ones with a mixture of the first 2 patterns - lymphoplasmacytic lichenoid, interface dermatitis with hydropic degeneration. The authors then evaluated whether the group responded to antibiotics or immunomodulating therapy. There was no statistical difference when histopathologic features were compared between the 2nd and 3rd groups! The author now believes that all cases of canine nasal dermatitis should have a 30 day course of cephalexin prior to immunomodulating therapy- in fact prior to biopsy a 3-4 week course of a cephalosporin is appropriate and may establish a diagnosis without needing to biopsy the lesion!

A better way to approach cases of nasal dermatitis that presents clinically as the “typical” DLE is to recognize that is a reaction pattern rather than a disease. This reaction pattern (lymphoplasmacytic lichenoid nasal dermatitis) may be antibiotic responsive or may require immunomodulating therapy. Since the biopsy findings will be identical in both cases, a 30 day trial of a cephalosporin prior to biopsy should be administered.

Diagnosis
Dogs with DLE are clinically healthy and are normal hematologically and serologically (including a negative ANA). Historically the histopathologic changes consistent w/DLE included a lymphocytic to lymphoplasmacytic lichenoid interface dermatitis w/hydropic degeneration of basal keratinocytes. Scattered apoptotic keratinocytes may also be present. Failure to respond to a 30 day course of a cephalosporin is also required for the diagnosis.

Treatment
When treating dogs with DLE it is important to avoid aggressive therapy since it is primarily a cosmetic disease. Occasionally the lesions seem to bother the dog because of pruritus. It is therefore important to treat cases in proportion to the severity of the symptoms. Be sure that the therapy is not worse than the disease. The author treats this disease in a stepwise progression with each step added to the previous therapy except where noted. The steps are as follows: Cephalexin 10-15 mg/# bid- tid for 30 days (since DLE and MCP are indistinguishable); if the dog does not respond to the cephalexin, then the cephalexin is discontinued and the following treatment is begun, sun avoidance, sun screens and vitamin E and omega 3 fatty acids. Niacinamide and tetracycline are begun as previously described. If after 60 days the dog doesn’t respond to this treatment the next step is topical GC (beginning with a moderately potent GC). If after 60 days there is no response then stop the tetracycline and niacinamide and begin systemic prednisolone (anti-inflammatory doses) that is slowly weaned over a period of months to achieve the lowest possible dose.

The mite Demodex spp., which belongs to the Class Arachnida, Order Acarina, lives in hair follicles of all mammals. Demodex canis is the dog follicular mite while in cats it is D. felis (in cats). In dogs Demodex injai is found within sebaceous glands and ducts. D. cornei and gatoi live in the stratum corneum of dogs and cats respectively. They complete their life cycle in about 30 days and the adults will survive for about 21 days. The life cycle of demodex is that an egg (fusiform shaped) develops into 6 legged larvae that then develops into an 8 legged nymph (differentiated from an adult by its lack of an "armor-like" breastplate). This nymph then matures into an adult.

Neonates are thought to acquire mites from their dam/queen via direct skin-to-skin contact during nursing. Direct transmission, other than from dam/queen to the pup/kitten, only occurs with D. gatoi in cats.

In a normal animal the mite does not cause any symptoms. However in some dogs it may cause either localized or generalized disease. There is no universally accepted definition of localized vs generalized disease but recently it has been suggested that with localized disease there are no more than four lesions with a maximum diameter of to 2.5 cm; Demodicosis is also categorized based on age of onset: those less than 12 months of age (18 months in large or giant breeds) are considered juvenile onset while older dogs are considered adult onset. The prognosis is excellent for the localized form either in puppies or adult dogs while the generalized form carries a more guarded prognosis.

Demodex causes disease when there is an overgrowth of the commensal mites either associated with a genetic defect (juvenile onset) or immune suppression (adult onset). In the adult dog, hyperadrenocorticism (iatrogenic or spontaneous), hypothyroidism, leishmaniasis, or chemotherapy are the most identifiable causes of adult onset generalized demodicosis. Note that contrary to what was previously taught, “dogs with adult onset demodicosis have cancer or some other very serious life threatening disease”, in the author’s experience, idiopathy is the rule not the exception. In a retrospective study, less than 50% of the adult onset generalized demodicosis cases had an identifiable underlying cause.

The lesions associated with demodicosis include non pruritic alopecia, scaling, follicular casts, follicular papules/pustules (if a secondary bacterial infection is present), comedones, crusts, erythema, hyperpigmentation, and lichenification. Pruritus is variable but is mild except in cases with a secondary bacterial folliculitis.

Lesions frequently involve the face and/or forelegs and may progress to affect other body sites. Since the lining of the external ear canal is epidermis, demodicosis may cause a bilateral ceruminous otitis externa. As the disease progress dogs may develop a deep bacterial folliculitis and furunculosis and draining tracts. In those cases peripheral lymphadenopathy, lethargy and fever are commonly present. In some patients their presentation is exclusively pododemodicosis. In these cases a deep bacterial folliculitis and furunculosis is frequently present and the feet are swollen and painful leading to lameness.

In contrast to D.canis and cornea, D. injai tends to be associated with a greasy hair coat on the dorsum of the trunk. Many times alopecia is not present and only a low number of mites may be found on skin scrapings. It has been reported that terriers, especially wire haired fox terrier and West Highland white terrier, are at risk of developing this form of demodicosis.

Since demodicosis is a folliculocentric disease it will look identical to follicular lesions caused by a bacterial pyoderma and dermatophytosis. Because of the similarity in appearance these folliculitides, clinical appearance is not an acceptable method to rule-in or rule-out demodicosis. Superficial (for D.cornea) and deep skin scrapings (for the other species of demodex) are the most reliable and cost effective method to diagnose demodicosis. In medium or long haired dogs, clip a small “window” in the hair coat to get easier access to the skin and to prevent the loss of the scraped material into the surrounding hair. Skin scrapings are performed with a No. 10 scalpel blade after dulling the blade on the frosted end of the microscope slide.

To perform a deep skin scraping it is best to squeeze the skin prior to and during the scraping to push the mites out of the hair follicles. Scrape the skin in the direction of hair growth until capillary bleeding occurs. When lesions are present on the face or paws the animal should either be sedated before scraping or a hair pluck/trichogram may be performed in an awake animal. Hair plucks are performed with mosquito hemostat forceps that grasp and pull out hairs. It is best to collect hairs from the leading edge of the lesion. To increase your yield, squeeze the skin as you are plucking the hairs and be sure to collect a large number of hairs (50–100). Take the collected hairs and lay them on a slide containing a drop of mineral oil and add a cover slip. Sample multiple sites in each patient. Trichograms, or in cases of pustular demodicosis examination of the exudate, will detect Demodex mites in about 85% and 100% of dogs respectively with demodicosis. If the trichogram is negative but other sites are positive, sedation and skin scrapings of the feet should be performed since the mites may be present even if the feet appear alesional. It has been the author’s experience that pododemodicosis, if present, is usually the hardest component of generalized demodicosis to resolve and so should be used as one of the monitoring sites.
Recently it has been reported that applying tape to a skin lesion and then squeezing the skin is as an effective way to identify demodex mites in dogs. A study was performed to confirm this observation. Specifically, the study was to evaluate and compare the sensitivities of acetate tape impression deep skin scraping for the diagnosis of canine demodicosis. They concluded that squeezing the skin followed by acetate tape prep was found to be as sensitive as deep skin scraping for the diagnosis of canine demodicosis. Unfortunately the author has not had the same experience. So if you want to do it as a screening test, in difficult to handle dogs or sensitive locations on the dog, be sure to follow it with deep skin scrapings (with sedation if needed) if the tape prep is negative.

Be sure to collect samples from multiple sites and note the site that the sample is collected from since localized disease is treated differently than generalized disease. When examining the slides you need to evaluate for the approximate number of each stage that is present (eggs, larva, nymph and adults). Also note how many of the mites alive vs are dead. These results will be important to compare to future mite scrapings as you are monitoring the dog’s response to therapy. With effective treatment a decreasing number of immature mites and the disappearance of eggs should occur. The number of live mites should also decrease. In all cases of demodicosis be sure to perform an examination of an otic swab. Otodemicosis is identified by collecting roll swabs from each ear using a cotton swab that has been dipped in mineral oil. The sample collected is place onto a glass slide that also has a drop of mineral oil on its surface. A cover slip is applied and then the sample is examined.

If samples are collected as described it would be extremely uncommon to miss the presence of demodex mites. Occasionally this may occur, even with properly performed skin scrapings and hair plucks, if the dog has scarring due to chronic disease or because of the thickness of their dermis (therefore the deeper depth of their hair follicle making expulsion of the mite more difficult) (ie, Shar-Pei). If demodicosis is strongly suspected, but no mites are found on skin scrapings and hair plucks, skin biopsy is recommended to rule in or rule out their presence.

How to treat a dog with demodicosis depends on whether it is localized or generalized. In cases of localized demodicosis, less is best. In many cases, especially juvenile onset, the disease will spontaneously resolve within a couple months. Miticidal therapy is not required unless the disease becomes generalized. Since the progression of localized disease to more generalized form is not influenced by whether the localized form is treated or not, treatment of localized disease is not necessary. However, in the author’s practice “benign” topical treatment is prescribed. This is done so that if the disease does progress, the owner feels that something had been done to try to prevent for occurring. Topical therapy with benzoyl peroxide shampoo and/or gel can theoretically be helpful due to its antibacterial properties and follicular flushing activity. Due to its suppressive effect on the immune system you should avoid using any steroid containing product (topically or systemically) in patients with demodicosis (localized or generalized). Ensuring a proper diet and intestinal deworming program should also be part of the treatment of dogs with demodicosis. To evaluate the effectiveness of treatment, a follow up examination, including repeating skin scrapings, should be performed in 30 days.

Treating a dog with generalized demodicosis requires much more aggressive therapy than localized. Multimodal therapy, a common approach that is used to treat other diseases (eg arthritis, atopic dermatitis or congestive heart failure) will be necessary when treating generalized demodicosis. Acaricidal therapy and treating secondary bacterial infections if present is required for both adult and juvenile onset disease. In adult onset cases attempts should be made to identify and treat the underlying systemic disease.

Dogs with juvenile onset generalized demodicosis, in addition to the above mentioned treatment should be neutered. This is important not only to prevent the propagation of this genetic defect but also estrus may trigger recurrence of clinical disease. As mentioned previously, in cases of adult onset generalized demodicosis attempts should be made to identify and treat the underlying disease. Evidence shows that successful treatment of an underlying cause increases the likelihood that adult onset demodicosis can be cured. In the author’s practice, diagnostics performed in cases of adult onset generalized demodicosis include a CBC, serum chemistry profile and a urinalysis. Depending on the age of onset, abdominal ultrasound and thoracic radiographs may be included in the minimum database. Because of the influence that bacterial pyoderma or generalized demodicosis has on evaluating thyroid or adrenal gland disease, evaluation of these organs is delayed until any secondary bacterial infection has been resolved and the demodicosis has improved or is in remission.

Specific treatment of generalized demodicosis is outlined in Table 1. This table is the result of the most recent consensus guidelines written by an international group of dermatologists. The author has indicated in bold the approach used in his practice. However other therapies have come to the forefront since these guidelines have been published. Specifically the isoxazolines class of ectoparasiticides (fluralaner, afoxolane and, sarolaner). These products have a broad spectrum of insecticidal and acaricidal activity. Besides their efficacy against fleas and ticks, there are limited studies reporting the effectiveness of these drugs against a variety of mites including demodex, sarcoptes and otodectes. Given their ease of use and safety many practitioners are using these products as a first line treatment for canine demodicosis. The following is the most current information concerning these products effectiveness against canine demodicosis.
Fluralaner (Bravecto) - a study was done in 2015 that compared the efficacy of oral Bravecto™ (fluralaner) with the efficacy of topically applied Advocate/Advantage multi® (imidacloprid/moxidectin) for the treatment of generalized demodicosis (GD) in dogs.

In this study 16 dogs, all over 12 months of age that had been diagnosed with generalized demodicosis, were randomly assigned to being treated with either 1 dose of fluralaner or 3 doses (q 28 days) of imidacloprid/moxidectin. Dogs were examined (and had skin scrapings) at the beginning of the study and then every 28 days for 12 weeks. The results revealed a 99.8% reduction in mite numbers on Day 28 and 100% on Days 56 and 84 after 1 dose of fluralaner. Mite numbers in the dogs treated topically on three occasions at 28-day intervals with imidacloprid/moxidectin were reduced by 98.0% on Day 28, by 96.5% on Day 56 and by 94.7% on Day 84. The biggest drawback in this study was that the dogs were only followed up for 12 weeks so that we don’t know the relapse rate. Since juvenile onset GD has a higher success rate than adult onset GD it would have been beneficial to stratify the dogs into 2 groups based on age of onset.

Also in 2015 another study evaluating the efficacy of fluralaner for the treatment of canine demodicosis was reported. One hundred sixty three dogs of different breeds with GD. Animals were divided into two age groups based on age at presentation: group one, 2–18 months (62.6%) and group two, over 2 years of age (37.4%). Dogs were treated with fluralaner (25 mg/kg) orally, twice three months apart. Skin scraping and/or hair plucking were performed 1, 2 and 3 months after the first fluralaner administration. The overall response to therapy was 100%. The majority of dogs (87.1%) had negative skin scrapings at the 30 day exam (note that this was an abstract so they didn’t state if the negative skin scraping was only in reference to live mites or to any stage or fragment of a mite). Twenty-one individuals (12.9%) (all belonging to group two) needed two months after the initial fluralaner administration to achieve negative scrapings. As with the previous study, no long term follow up was performed so relapse rate is unknown. Note even though the drug insert states that the dog needs to be > 6 months old to administer fluralaner the label in Europe states it should not be used on puppies less than 8 weeks old and/or dogs weighing less than 2 kg. The FOI sheet states that it is not a safety issue, that the margin of safety in 8 week old puppies is adequate but substantial evidence to support a 12-week duration of effectiveness in dogs less than 6 months of age has not been demonstrated.

Because fleas are a concern in the authors practice and many of these dogs need frequent bathing initially the author used a combination of ivermectin daily and 1 dose of Bravecto every 3 months. Note that it has been shown that the concurrent administration of fluralaner and ivermectin (0.3 mg/kg) does not alter the pharmacokinetics of either compound. Based on the plasma pharmacokinetic profile and the clinical observations, there is no evident interaction between fluralaner and ivermectin, and co-administration does not increase the risk of ivermectin associated neurotoxicity. The response to this combination was less than that of the studies previously discussed so this practice has been discontinued. It is theorized that because Bravecto is a selective inhibitor of arthropod γ-aminobutyric acid- and l-glutamate-gated chloride channels and ivermectin's mechanism of action is that it enhances the effects of glutamate at the invertebrate-specific glutamate-gated chloride channel, with minor effects on gamma-aminobutyric acid receptors.

Afoxolaner has also been studied for treatment of generalized demodicosis. A 3 month study was performed in which 16 dogs with generalized demodicosis were divided into 2 treatment groups. In the first group the eight dogs were treated w/afoxolaner (NexGard®) at the label dose but given every 14 days (days 0, 14 and 28) and then 1 monthly treatment (day 56). The other 8 dogs were treated with topical imidacloprid/moxidectin (Revolution/Advocate®, Bayer) at the same treatment interval. The mite reduction is listed below.

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99 Karas-Tecz J, Dawidowicz J Efficacy of fluralaner for the treatment of canine demodicosis , Veterinary Dermatology,2015; 26, 307

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195
Table 4. Mite count reduction in treated groups (based on geometric means).

<table>
<thead>
<tr>
<th>Day</th>
<th>Group 1 – Imidacloprid/moxidectin</th>
<th></th>
<th>Group 2 – Afoxolaner</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geo mean</td>
<td>Reduction (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>0</td>
<td>808.1</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>28</td>
<td>82.4*</td>
<td>89.8</td>
<td>0.0008</td>
</tr>
<tr>
<td>56</td>
<td>119.9*</td>
<td>85.2</td>
<td>0.0013</td>
</tr>
<tr>
<td>84</td>
<td>108.5*</td>
<td>86.6</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

* Group 2 differed statistically significantly (\( p < 0.05 \)) from group 1.

There were statistically significantly fewer mites found on Days 28, 56, 84 in the afoxolaner group. The authors concluded that afoxolaner given orally every 2 weeks for 3 treatments, then monthly is highly effective against generalized demodicosis, within 2 months BUT a few things to point out: The study states that On Day 84, no live mites were recorded for any dog in the Nexgard–treated group- the key word is LIVE mites. This is apparent because later in the article it states that a significant portion of the afoxolaner-treated dogs (7/8) had no mites in their skin scrapings at Day 84. So I interpret this to mean that at day 84 there were still mites present on the 1 dog treated with Nexgard, perhaps dead or maybe fragments of the mite. This impression is further supported by the statement that “in the present study, seven out of eight NexGard–treated dogs had two successive negative skin scrapings at a one-month interval, indicating that treatments at appropriate intervals can provide remission of the disease”. So the key to this is that there needs to be 2 consecutive negative skin scrapes to declare the demodicosis in remission so not all dogs were in remission. Other issues are they didn’t say how old the dogs the dogs were other than > 6 months of age – it is important to stratify the groups into adult and juvenile onset as the later is in general more difficult to get in remission and in fact juvenile onset generalized demodicosis may self cure. They didn’t state if any of the dogs had previously been treated for demode- only that they had not received an ectoparasiticide or macrocyclic lactone for at least 12 weeks prior to Day 0, as far as it could be reasonably established by verbal communication with the owners. Lastly they didn’t state how long the dogs had generalized demodicosis before entering into the study.

There was another study\(^1\) using afoxolaner for the treatment of generalized canine demodicosis that involved 4 dogs- ages 8 months to 10 years of age. All dogs had been affected for at least 2 months. These dogs were treated at label dose on day 1 then at 4 weeks and 8 weeks after the initial dose. There was a reduction of live mites by week 4. All 4 dogs were negative for live mites 8 and 12 wks after treatment. The problems with this study are the same as the previous study using afoxolaner other than it did state that the dogs were affected for at least 2 months with generalized demodicosis. The author reported that at the time of preparation of the paper, 6 months after the initiation of treatment with afoxolaner, all four dogs remain clinically free from clinical signs of demodicosis. The problem is that it has been shown that clinical remission is not the same as parasitic remission – the later be required to state that the dog is in remission and can only be determined by skin scrapings.\(^2\) Note that the product insert contains a caution about use in dogs with a history of seizures.

Sarolaner was recently studied\(^3\) where it was compared to topical imidacloprid-moxidectin for the treatment of generalized demodicosis. Sixteen dogs over the age of 6 months were entered into the study. The dogs were divided into 2 groups - group 1 was treated w/sarolaner orally on days 0, 30 and 60 while the other group was treated with the topical imidacloprid-moxidectin weekly. Efficacy for sarolaner based upon live mite counts was 97.1% and 99.8% on Days 14 and 29, respectively and 100% on all subsequent days. For the topical therapy group efficacy based upon live mite counts was 84.4%, 95.6% and 99.7% on Days 14, 29, and 44, respectively and 100% on all subsequent days. Limitations of this study were they only followed up for 30 days after the last treatment so we don’t know the relapse rate. Since juvenile onset GD has a higher success rate than adult onset GD it would have been beneficial to stratify the dogs into 2 groups based on age of onset. They didn’t state if any of the dogs had previously been treated for demodex and lastly they didn’t state how long the dogs had generalized demodicosis before entering into the study.

Two studies have evaluated the efficacy of doramectin in the treatment of generalized demodicosis.\(^4\),\(^5\) Both studies used a dose of 0.6 mg/kg body weight given every 7 days; in the first study the drug was administered by subcutaneous injection to 23 dogs

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and in the second it was administered orally to 29 dogs. Administration subcutaneously appeared to be marginally more effective but the cohort size in each case was relatively small and thus caution needs to be exercised in the interpretation of results. It has been shown that subcutaneous injection of doramectin results in slower drug absorption and greater bioavailability of the drug compared to oral administration. A study therefore was performed in which 400 dogs with generalized demodicosis were treated using weekly s.c. injections of doramectin at a dose rate of 0.6 mg/kg body weight. Results revealed that 66.7% of the dogs over the age of 4 achieved remission by having two consecutive negative skin scrapings while the overall remission rate based on intent to treat was 86.3%. This may be a good option for those dogs in which people are unable to give oral ivermectin due to the taste of the ivermectin.

It is interesting that when you look at any of the treatment protocols it seems none are 100% effective so the bottom line is to start with the easiest, safest and least expensive treatment and if that is ineffective to try another treatment.

Remember, regardless of the selected treatment, miticidal therapy should be followed up with skin scrapings since dogs may look normal clinically but still have active disease (as determined by the presence of mites on skin scrapings) treatment must be continued beyond clinical resolution. Parasitic cure is defined as multiple negative skin scrapings, including lack of dead or fragmented mites, on 3 consecutive monthly visits. Skin scrapings should be used to determine the therapeutic end-point. This end point is reached when the dog looks normal clinically and skin scrapings have been performed monthly ALL areas that have EVER been positive on skin scraping and have been negative for 3 consecutive visits. If during a visit the skin scraping is positive, it is important to compare the number of live and dead mites and the number of each stage of the mite life cycle to the previous visit. An indication of effective treatment is that during therapy the number of live mites found on skin scrapings and the number of immature mites should be reduced beyond clinical resolution.

Diagnosis and treatment of demodicosis is an important concept that all small animal practitioners should feel comfortable with. By taking time to thoroughly examine and evaluate the dog, and spending time explaining the disease to the owner, the outcome will usually be successful.

Table 1- Summarized treatment of canine demodicosis *(Items in bold are the author’s preferences)*

<table>
<thead>
<tr>
<th>Treatment of a dog with severe generalized disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Perform cytology and if there is evidence of a deep bacterial skin infection or the dog has been treated previously with antibiotics a bacterial culture and sensitivity. With inflammatory cells and bacteria present, appropriate oral antibiotic therapy is required.</td>
</tr>
<tr>
<td>2 Use topical therapy with chlorhexidine or benzoyl peroxide shampoo weekly to possibly twice weekly. (Unless amitraz is being applied)</td>
</tr>
<tr>
<td>3 There are several treatment options for the treatment of canine demodicosis. The best option will depend on the legalities pertaining to the use of veterinary pharmaceutical products in the country of residence, the finances of the owner and the clinical situation. However, independent of the treatment specifics the dog should be neutered because dogs in need of mite treatment should not be allowed to breed, and the disease may relapse in cycling bitches.</td>
</tr>
<tr>
<td><strong>a. Ivermectin</strong> at an oral dose of 0.3–0.6 mg/ kg (0.4 mg/kg) or moxidectin at 0.2–0.5 mg/kg p.o. daily are further options. Note: many herding breed dogs have a genetic predisposition to adverse drug reactions involving ivermectin due to a defective MDR-1 gene. This gene is responsible for pumping drugs out of the mammalian’s brain. When this gene is defective, drugs accumulate in the brain leading to adverse events. Gene testing for the defect can help eliminate at risk dogs but there are a number of dogs with adverse effects to ivermectin and an intact MDR-1 gene due to alternative mechanisms. Thus adverse events may still occur in dogs with normal MDR-1 genes. Therefore with both drugs, a gradual increase from an initial dose of 0.05 mg/kg to the final dose (of 0.4 mg/kg) within a few days is recommended to identify dogs that cannot tolerate those drugs. Monitoring for neurological adverse effects should occur throughout the course of therapy. Ivermectin is the treatment of choice in the author’s practice.</td>
</tr>
<tr>
<td><strong>b. Amitraz</strong> weekly or every 2 weeks in a concentration of (0.025–0.06%) can be used. Dogs with a medium to long hair coat need to be clipped, and skin should stay dry between rinses to avoid washing off the drug. Rinsing should be performed in well-ventilated areas. The author only uses this therapy if the dog has failed to respond to ivermectin or is a herding breed. Please note that amitraz is EPA registered and doesn’t EVER allow any off label use (label states 1 bottle/2 gallons every 14 days)</td>
</tr>
<tr>
<td><strong>c. Milbemycin oxime</strong> may be administered orally at a dose of 1–2 mg/kg/day. Moxidectin orally (see below) is in the milbemycin family, is much less expensive than milbemycin, and is used if the dog fails to respond to ivermectin (again a non herding breed)</td>
</tr>
</tbody>
</table>

d. Moxidectin as a spot-on in combination with imidacloprid may be used weekly. This spot-on formulation has a markedly higher success rate in dogs with milder disease or juvenile onset.

e. Doramectin weekly at 0.6 mg/kg p.o. or SQ is a possible treatment. A gradual increase from an initial dose of 0.1 mg/kg to the final dose seems prudent to identify dogs that cannot tolerate the drug and will show neurological adverse effects. (SEE PREVIOUS DISCUSSION ABOVE ABOUT PO VS SQ)

So to summarize - this report states that “There is good evidence for the efficacy of weekly amitraz rinses and daily oral macrocyclic lactones such as milbemycin oxime, ivermectin and moxidectin for the treatment of canine demodicosis.”

Other recommendations are:

- Dogs should be evaluated monthly, and treatment should be continued until 3 consecutive visits with multiple negative skin scrapings have been achieved.
- Treat secondary bacterial infections
- Factors predisposing to demodicosis, such as malnutrition, endoparasites, endocrine disease, neoplasia and chemotherapy, should be identified and corrected to maximize response to therapy.

Every spring, the American College of Veterinary Dermatology (ACVD) and the American Academy of Veterinary Dermatology (AAVD) host a North American Veterinary Dermatology Forum (NAVDF). This last NAVDF was held in Orlando, FL in April 2017. The NAVDF is open to everyone with an interest in veterinary dermatology, including both boarded and non-boarded veterinarians, technicians and veterinary students. The three-day conference presents the latest research in veterinary dermatology as well as clinical updates to aid veterinarians and specialists in diagnosing and treating dermatologic diseases. Many of the research abstracts and poster presentations presented at the NAVDF will not be published for months to years after the conference, so I have tried to summarize the more clinically relevant information. The notes for this lecture were due before the conference was held so I summarized some of the most timely and important topics that are being researched and discussed at the NAVDF and other large Veterinary Dermatology conferences.

**Atopic dermatitis/pathogenesis**

The most recent definition of canine atopic dermatitis (CAD) as proposed by the International Task Force on Canine Atopic Dermatitis is: “A genetically predisposed inflammatory and pruritic skin disease with characteristic clinical features associated with IgE antibodies most commonly to environmental allergens”. Canine atopic dermatitis is a genetically predisposed and multifactorial disease involving immune dysregulation, allergic sensitization, skin barrier defects, microbial colonization and environmental factors. Approximately 10% of cases that present clinically as classical CAD have no measurable allergen-specific IgE; these cases are called Atopic-like Dermatitis (ALD).

Increased risk factors of developing AD include living in urban areas, exposure to dense human population areas, early adoption of bathing and regular bathing. Living in a rural environment, living with other animals and non-commercial diets appear to be protective. In the study of human AD a theory called the hygiene hypothesis has been proposed where certain macrobiotic diets, probiotics, endotoxins and micro-organisms reduce the incidence of human AD.

As in human AD, studies in dogs have shown that skin barrier function is important in canine AD. Removing part of the stratum corneum through tape-stripping enhances house dust mite allergen specific IgE levels, intradermal test reactions, and peripheral T-cells responses. Transepidermal water loss (TEWL) is also higher in atopic dogs than in healthy controls. The stratum corneum of atopic dogs is thinner with wider intercellular spaces. The lipid layers important in protection of the skin are shorter, thinner and irregular in atopic dogs compared to healthy dogs. Changes to the balance of lipids in the skin of atopic dogs has been shown with reduced levels of ceramides 1 and 9 and increased levels of cholesterol.

The development of a healthy barrier function is complicated and associated with keratinization. An important molecule in this process is filaggrin. In some people with AD, a genetic defect in filaggrin is present. In a Beagle model of AD, filaggrin immunostaining was significantly lower in atopic compared to healthy dogs. Another study found that 22% of atopic dogs appeared to have a mutation in their filaggrin.

**New therapies for atopy: Immunotherapy**

In allergen-specific immunotherapy (ASIT) extracts of allergens to which the patient is sensitive are given gradually to decrease the allergic response. Unlike drug therapies, ASIT is the one proven treatment for allergies that change the patient’s immune response rather than blocking inflammatory mediators. ASIT is appealing as it is associated with very few adverse effects and is effective in the majority of patients at some level. Challenges with ASIT include a prolonged time to effect and requires subcutaneous injections, which owners are sometimes hesitant to perform.

There are many theories on how ASIT works including the following: the blocking antibody theory, where IgG is produced, competing with IgE and the immune deviation theory, where T helper lymphocytes types are altered. ASIT has also been shown to down regulate mast cells and eosinophils and increase numbers of anti-inflammatory mediators like regulatory T cells, IL-10, and TGF-beta.

Sublingual Immunotherapy (SLIT): Sublingual immunotherapy (SLIT) involves administration of allergen extract into the mouth, to expose the allergen to the oral mucosa. SLIT has become a common form of immunotherapy in Europe for people with allergic rhinitis and asthma. Studies on the efficacy of SLIT in people show varying degrees of success, possible due to large variability in treatment protocols although overall, SLIT in people has shown to be effective and safe. There have been several small studies looking into SLIT in dogs with AD and several companies are now offering it (HESKA ALLERCEPT® Therapy Drops, SkinVet™
RESPI™ Oromucosal spray, NelcoVet Allerpaws oral allergy treatment. SLIT protocols use glycerin-preserved extracts applied under the tongue or between the cheek and gum once or twice daily, where it can taken up by oromucosal dendritic cells.

Recent trials of SLIT in dogs have shown variable efficacy as in people, again possibly likely to differences in protocols. An initial pilot study by Dr. DeBoer in mite-sensitive dogs was used a protocol modified from human SLIT methods showed clinical improvement in the majority of dogs with reductions in mite allergen-specific IgE and increases in allergen-specific IgG. This same group has conducted a larger study with 174 atopic dogs evaluated. They concluded that SLIT is effective in approximately 60% of patients. There is some evidence that SLIT can be effective in a percentage of patients who have failed standard ASIT. A double-blinded, controlled study by another group evaluated 18 atopic dogs and found 66% had greater than 40% improvement in clinical signs after a year of SLIT. However, 50% of control dogs also had greater than 40% improvement. Although SLIT in dogs has shown some promise in treating AD, there is more evidence based medicine as well as clinical experience with standard ASIT based on allergy testing. We will likely see more research on the best protocols for performing SLIT in dogs as well as more well-designed clinical trials to better prove its efficacy in the coming years.

HESKA ALLERCEPT® Therapy Drops are currently only available through a veterinary dermatologist but will likely be released to veterinarians soon. Allergy testing is needed through either intradermal allergy testing or serology testing to identify specific allergens. Allergens can be ordered through HESKA with twice daily administration. SkinVet™ RESPIT™ Oromucosal spray is administered once daily and does not require allergy testing since it uses regionally important allergens. NelcoVet Allerpaws oral allergy treatment is once daily and can be formulated on results of allergy testing or can be formulated using requested allergens.

**New therapies for atopy: Medications**

Stem Cell therapy: The most commonly studied and utilized stem cell type in veterinary medicine are mesenchymal stem cells (MSC), which can be harvested relatively easily from bone marrow and adipose tissue. MSC have been used primarily in orthopedic applications but new research is looking into using them for both atopic dermatitis and auto-immune diseases like pemphigus. Studies are ongoing for allogenic stem cell products that can be mass produced for immediate and “off-the-shelf” access. Human trials have used IV stem cells to treat multiple sclerosis, rheumatoid arthritis and lupus. In vivo studies have shown stem cells to aid in wound repair. In the next few years, look for new studies on the use of MSC in veterinary dermatology.

Oclacitinib: Pfizer Animal Health is working on a new medication for canine AD called Oclacitinib. It development is based on research showing the importance of the cytokine IL-31, which is released by T lymphocytes and is implicated in human atopic dermatitis. Oclacitinib is a selective janus kinase (JAK) inhibitor that blocks the pruritogenic effects of IL-31. Several abstracts were presented at WCVD presenting clinical trial data. A multi-center placebo controlled study with 341 dogs (0.4 mg/kg q12h for 14 days) found significant reductions in pruritus and clinical scores with GI signs (vomiting and diarrhea) the most common side effect. Another study compared oclacitinib and prednisolone in two models or itchy dogs (those injected with Il-31 and those with flea allergy dermatitis) and found oclacitinib to have a faster onset and greater suppression of itch than prednisolone in both groups.

Cytopoint™ is a monoclonal antibody that targets and neutralizes IL-31. IL-31 is an important interleukin that has been shown to be important in contributing to itch in atopic dogs. Cytopoint™ is labeled for use in dogs (NOT IN CATS) given as a SQ injection to block itch. The injection lasts for most dogs for 4-8 weeks. We have also been part of the clinical trials for Cytopoint™. In our experience, it may last even longer but also much shorter, or not at all, in some dogs. We have found Cytopoint™ to be effective in some dogs where other modalities have failed and its safety makes it helpful for dogs that may need other medications to control their allergies.

**New therapies: Barrier function aids**

Shampoos, lotions and conditioners can be useful in increasing skin moisture, decreasing pruritus and removal of superficial pathogenic bacteria and yeast. In dogs, a double blinded randomized controlled trial showed that a weekly bath with a 10 min application of a shampoo containing ceramides, essential fatty acids, monosaccharides and alkyl polyglycosides (Allermyl®, Virbac) led to a 50% reducing in pruritus scores within 24 hours in 25% of treated. Another study using a weekly bath with Allermyl® shampoo (Virbac) in allergic dogs showed reductions in pruritus, clinical scores and TEWL. Another study looking at twice weekly bathing for 4 weeks with a medicated shampoo containing chlorhexidine, lactoferrin, piroctone olamine, chitosan and essential fatty acids showed significant improvement in pruritus. However, the same improvement was also seen in the control shampoo. This study and others indicate that shampooing in general can help in treatment of atopic dogs and that some shampoos may be better than others.

Topical fatty acid application: The use of topical compounds containing mixtures of skin lipids found in the stratum corneum (cholesterol, free or essential fatty acids, and ceramides) has become a popular therapy for AD. Several recent studies have shown encouraging results using these spot-on therapies with improvement in histological changes in atopic canine skin after 18 days of treatment with a compound containing ceramides, free fatty acids and cholesterol (Allerderm®, Virbac). A more recent study using a weekly spot-on formulation (Dermoscent Essential 6®, LDCA) containing essential oils and unsaturated fatty acids and a daily spray (Dermoscent Atopt 7®, LDCA) containing similar ingredients to the spot-on for 8 weeks showed a significant decrease in clinical
scores and pruritus. A larger study using Dermoscent Essential 6® applied once weekly for 8 weeks showed improvement in clinical scores and pruritus compared to control (placebo) dogs. Since these products must incorporated into the stratum corneum, they may take several weeks before becoming effective.

New therapies: Hydrolyzed diet
Royal Canin has introduced a relatively new hydrolyzed dry diet called Ultamino where 100% of the novel protein source is under 1kDa in weight with 88% free amino acids and very low molecular weight oligopeptides. The parent protein is feather protein, hydrolysed using a method developed for human products where free amino acids are required. The carbohydrate source is purified maize starch, which contains no protein. Most of the proteins (95%) are less than 1 kDa, which is much smaller than other hydrolyzed diets on the market. A clinical study in 22 dogs with presumed food allergy showed all dogs showing improvement in their clinical and pruritus scores.

Staphylococcal pyoderma
Multi-resistant bacteria: Antimicrobial resistance is becoming a problem in veterinary medicine as it has become in human medicine. Methicillin-resistant S. pseudintermedius (MRSP) carries the mecA gene, which encodes for a mutant penicillin binding protein, which prevents binding of beta-lactam antibiotics. A study first presented in April 2011 looked at 165 dogs with pyoderma cultured and found that over 50% of cases were resistant strains of Staph. After treatment with appropriate antibiotics dogs with sensitive strains of Staph. These dogs were re-cultured and 31% were found to harbor a resistant strain, indicating that acquisition of MRSP during treatment appears to be common. These authors also found that persistence of MRSP on skin and carriage sites is common after the resolution of MRSP pyoderma.

The recently formed Working Group on Antimicrobial Guidelines by the International Society for Companion Animal Infectious Disease (ISCAID) has come up with some guidelines about bacterial culture and antimicrobial susceptibility testing. They recommend bacterial culture be performed in the following cases: if there is a poor response to two weeks of appropriate systemic antimicrobial therapy, if there is emergence of new lesions two weeks or more after the initiation of such therapy, if there are residual lesions after six weeks of therapy combined with cytology demonstrating infection with coccoid bacteria or when cytology demonstrates intracellular bacterial rods.

Samples for culture should be taken from pustules if possible or taken from beneath crusts, or from papules or epidermal collarettes. Laboratories should differentiate coagulase positive and coagulase negative staphylococci and should be able to distinguish S. aureus.

First line drugs which for Staph pyoderma include clindamycin, first generation cephalosporins, potentiated sulphonamides, erythromycin, lincomycin and doxycycline. Second line drugs can be used when first line drugs are not effective (cefovecin and cepodoxime, fluoroquinolones, chloramphenicol and rifampin). In my opinion, third tier drugs, including vancomycin and linezolid, should not be used in veterinary medicine and saved for human use.

New therapies: Staphylococcus
An abstract presented at the WCVD looked at efficacy and adverse effects of rifampicin in canine pyoderma. They studied 19 dogs treated with rifampicin (5-11 mg/kg twice daily for 10 weeks), and found good response to the pyoderma but also GI signs and elevated liver enzymes in several patients. Rifampicin will likely be used more now in the face of MRSP/A infections, but monitoring should be performed. A new fluoroquinolone, called pradofloxacin is available for use in Europe and scheduled to be released in the US. pradofloxacin has good antimicrobial activity against gram positive bacteria, including Staph. An abstract showed good in vitro efficacy of pradofloxacin when tested against 60 isolates from dogs with pyoderma.
Some of the most common skin masses that can usually diagnosed with and FNA and in-house cytology include: vaccine reaction, follicular cyst, lipoma, histiocytoma and mast cell tumor.

**Vaccine reaction**
Vaccine reactions can occur at vaccination sites weeks or months following administration. These masses are subcutaneous and can be soft to slightly firm. The skin over these areas is usually normal. Cytology shows mixed inflammatory infiltrate of mostly lymphocytes and macrophages with some plasma cells, neutrophils, and eosinophils. Macrophages become activated with increased cytoplasmic basophilia, foamy cytoplasm, binucleated forms, and multinucleated giant cells. The key diagnostic feature is macrophages containing phagocytized vaccine adjuvant (seen as a bright pink, purple, or blue globular or granular material). These masses usually resolve spontaneously but can be surgically removed if needed.

**Follicular cyst**
Follicular cysts (epidermal inclusion cysts, epidermoid cysts) are nonneoplastic, noninflammatory, sac-like lesions lined by epithelium. Most canine and feline skin cysts are follicular cysts (arise from hair follicles) and include several histologic subtypes that are not cytologically distinguishable. These histologic subtypes have little clinical significance; they are benign and can be completely excised surgically.

FNA of follicular cysts will show abundant keratinocytes with possible cholesterol crystals, hair fragments, and activated macrophages. Within the preparation background, follicular cysts can also contain melanin granules that should be differentiated from bacteria. Cyst rupture and immunogenic keratin exposure to the dermis or subcutis can result in foreign body reaction with mild-to-marked infiltrates of neutrophils, macrophages, and multinucleated giant cells. Because, on cytology, a cyst cannot be differentiated from a cyst within a neoplasm (usually benign follicular neoplasm), histopathology is required to assess architecture; cytologic differentials include trichoepithelioma, infundibular keratinizing acanthoma, and pilomatrixoma.

**Lipoma**
Lipomas, benign neoplastic adipocyte growths, are typically soft, freely movable masses of varying sizes within the subcutis; however, infiltrative lipomas may be firmer and attached to underlying musculature. Before staining, lipoma preparations appear greasy and fail to air-dry. During staining, adipocytes may dissolve in the fixative to produce an acellular cytologic sample. If they do not completely dissolve in the fixative, adipocytes appear as large balloon-like cells arranged in aggregates held together by fine stroma. Individual cells are round to polygonal and contain a large, colorless intracytoplasmic vacuole that peripherally displaces a small, round, condensed nucleus. Complete surgical excision is curative.

**Histiocytoma**
Canine histiocytomas are benign, self-limiting dermal growths that usually occur on the ears, face, and distal extremities of young dogs. Histiocytomas can also occur in older dogs, but other tumors (other round cell tumors) should be considered. These lesions are frequently erythematous, alopecic, and dome-shaped with or without ulceration. On cytologic examination, many individualized, (irregularly) round histiocytes may display minimal or mild anisocytosis and anisokaryosis and contain some lightly basophilic cytoplasm that often stains paler than the platform background and is paler at the periphery as compared with that evident on perinuclear staining. A few punctate, colorless vacuoles may be noted. Nuclei are round to ovoid, variably placed in the cell, and display lacy chromatin with absent or occasional nucleoli. Varying numbers of small lymphocytes may be dispersed with increased lymphocyte numbers observed in regressing histiocytomas. Because histiocytomas cannot be cytologically differentiated from cutaneous or systemic histiocytosis, the latter conditions should be considered in dogs with multiple histiocytoma-like skin lesions.

**Mast cell tumor**
Canine mast cell tumors may be solitary or multicentric in the skin and can appear sequentially or simultaneously. They tend to be alopecic, erythematous, and varied in size. Ulceration may be present in larger masses, and the mass may change size as histamine is sporadically released from the neoplastic cells. On cytologic examination, these tumors frequently contain several mast cells and eosinophils with fewer neutrophils, fibroblasts, and collagen strands. Mast cells are round and individualized and contain lightly basophilic cytoplasm with few-to-numerous deeply basophilic intracytoplasmic granules. The degree of granularity depends on the granule’s staining characteristics, stain type, degree of cellular differentiation, and whether mast cells have recently degranulated in situ.

Often, the granules are so numerous that they physically obscure nuclear features or absorb so much stain that the nucleus stains pale. Diff-Quik may stain mast cells poorly or fail to stain the granules. If the granules do not stain, diagnosis can be achieved by
observing eosinophils mixed with round mast cells that display round, centrally placed nuclei and foamy or vacuolated cytoplasm. Any mast cell tumor should be considered potentially malignant, but greater nuclear pleomorphism (anisocytosis, binucleation) and observation of mitotic figures should increase concern for malignancy. Canine mast cell tumors should be surgically removed with wide margins and submitted for histopathologic evaluation and grading.

**Sebaceous masses**
Sebaceous masses (often adenomas) are “wart-like” masses and are often pedunculated and multilobulated, and they frequently develop on the head or dorsal trunk. FNA will show low cellularity, with rare sebaceous epithelial cells identified. Sebaceous hyperplasia and adenomas cannot be distinguished from each other by using cytologic examination alone; however, sebaceous adenomas are more likely to form a discrete mass.

**Squamous cell carcinomas**
These are very common tumors and the most common tumor of the head and neck of cats. Samples often contain a mixture of cell types because the neoplastic squamous cells are frequently accompanied by inflammatory cells (primarily neutrophils). Depending on the amount of inflammation, diagnosis can be challenging because squamous cells may become large and atypical as a result of the inflammatory process. The large epithelial cells are typically arranged in clusters or sheets. These cells may have a waxy, pale blue keratinized cytoplasm and a round nucleus with prominent nucleoli. Occasionally, cells may contain perinuclear vacuoles. Neutrophils are often observed coating the cytoplasm.
Cryotherapy in Practice
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Cryosurgery
Cryosurgery is the use of locally-applied extremely low temperatures to achieve selective destruction of tissues. Since the 1960’s, cryosurgery has gained popularity in both the veterinary and medical fields as an alternative to sharp surgical excision for certain benign and malignant cutaneous and subcutaneous tumors. Reported applications of cryosurgery in the veterinary field have ranged from ulcerative lesions of the integument and buccal cavity of mammals, reptiles, and birds, to anal furunculosis, papillomas, “mouth rot” in snakes, granulomas in all species, acral lick granulomas, equine sarcoids, tumors of the eyelid, interdigital cysts, ocular squamous cell carcinomas in cattle, melanocytic tumors, and squamous cell carcinomas of the feline nose. Reported use in man is even more extensive, including a wide range of benign and malignant tumors. As cancer is currently the major cause of pet animal death in the United States, and as skin and subcutaneous tumors are the most common and second most common tumor types in dogs and cats, respectively, cryosurgery can be an important and effective therapy in appropriate patients.

What are the principles behind cryosurgery?
The underlying principle of cryosurgery is that a cryogen (most commonly liquid nitrogen) acts as a heat sink to draw heat out from a local area of tissue and cause the tissue to freeze. Tissue that is subjected to cycles of freezing and thawing becomes damaged or destroyed. Subsequent cascades of inflammation, immune responses, and vascular stasis further this tissue damage. Cells are reliably destroyed at temperatures below -50 to -60°C.

There are four main ways that freezing and thawing contributes to tissue destruction. First, the formation of intracellular ice leads to cell rupture. Second, as the tissue freezes, solutes concentrate in the affected tissue, causing a chemical insult to the tissue. Next, inflammation contributes to tissue damage; and lastly, vascular stasis and thrombosis as a result of the cold result in the destruction of tissues. It has been theorized that certain immune responses may also be stimulated by the freeze-thaw cycle, which contributes to the remission of certain malignancies following cryosurgery.

How to perform cryosurgery
Instruments
The first instrument you will need is a cryogen. There are several types of cryogens available (see Table 1). Market availability, as well as the ability to reliably achieve the temperatures required for cell destruction, has made liquid nitrogen the most popular cryogen used today. The cryogen will be maintained in a specialized vessel (see Figure 1) that will need to be periodically refilled, depending on the type of container and cryogen used.

Next, you will need instruments to deliver the cryogen from the vessel to the patient. Four main delivery systems have been described (see Figure 2):

- The dipstick technique involves the use of a cotton swab onto which the cryogen is transferred. This cotton swab is then applied directly onto the lesion. This technique may be useful for small, superficial lesions. However, it has a low maximum freezing depth (2-3 mm) that makes it difficult to treat deeper lesions. In addition, certain viruses may survive in liquid nitrogen, necessitating separate allotments of cryogen for each patient treated with the dipstick method.

- The probe technique employs a probe tip that is cooled by circulating cryogen and applied directly to the lesion. The probe tips are available in a variety of sizes and shapes.

- The needle technique involves the use of a needle run through the deep tissue of a tumor. As the cryogen passes through the needle and vents to the surface on the opposite end of the needle, it forms an iceball around the needle in the deep portions of the tumor.

- The spray technique is the most popular. In this technique, a handheld spray unit with a reservoir of liquid nitrogen and a spray nozzle is directed toward the lesion. The clinician then directly sprays the lesion, either starting at the center and spiraling outwards towards the periphery of the lesion, or in a “paintbrush” pattern (moving the nozzle from one side of the lesion to the other as if spray painting a wall).

Additional instruments you may choose to employ include thermocouples and insulating plastic cones. Thermocouples are temperature probes placed at the lateral and deep margins as a means to evaluate extent of freezing. Insulating plastic cones are used with the spray technique. They are applied directly onto the lesions, helping to confine the spray of the cryogen to the area exposed by the cone and allowing a deeper depth of freeze of the affected tissue.

Freeze-thaw protocols
With any of the cryosurgery techniques, it is essential to achieve correct depth of freezing and temperature in the target tissue. The experienced clinician may feel comfortable evaluating the area and amount of freezing visually, with no additional instruments. More inexperienced clinicians may prefer the use of thermocouples. Recommended protocols to achieve correct freezing vary, partially
depending on tumor type, size, and location. Some clinicians recommend cryosurgery be performed only on tumors smaller than 2 cm in diameter; others suggest it can be used to treat larger tumors. Debulking before freezing is a well-accepted method that significantly improves cure rate for larger tumors.

Repeated freeze-thaw cycles to a minimum temperature of -50 to -60°C produce maximum destructive effects. For this reason, many clinicians perform 2 freeze-thaw cycles for benign lesions and 3 for more malignant lesions. Larger lesions require longer freezing times, though you should expect that this will also result in larger wounds and longer healing times. Some protocols recommend continuous freezing for 30 seconds, whereas others recommend intermittent freezing for 30-60 seconds until either thermocouple needles register -50°C or a halo of frozen tissue around the tumor is achieved. The halo of frozen tissue should range somewhere from 2 to 5 mm, depending on the specific type and malignancy of the tumor. The lesions should be allowed to thaw on their own (i.e. with no additional warmers to aid the thaw) to room temperature before the next freezing cycle is initiated. Halo thaw time in humans from an outer 5 mm border back to the tumor margin has been shown to take 60-180 seconds.

Treatment of benign epidermal lesions relies on mild freezing that results in separation of the epidermis from the dermis. Malignant lesions require a more rigorous freezing. However, as cellular components are more susceptible to cold injury than stromal components, the effects of cryosurgery are focused more on the malignant cells than surrounding tissues. Patients may occasionally require more than one session to fully remove the tumors.

Post-operatively, clients should wash the wounds gently with soap and water once or twice daily. Wounds should be left unbandaged, unless excessive drainage necessitates a dressing or unless self-trauma is a concern. An eschar will commonly remain on treated skin for a month after treatment. This eschar may be gently removed and an antibiotic ointment applied to the lesion base or underlying ulcer. Most non-malignant lesions will heal within 2-6 weeks; however, larger tumors or those on the trunk and extremities may take up to 12-14 weeks to heal.

Indications for cryosurgery
Benign, pre-malignant, and malignant tumors may be treated with cryosurgery. Each individual patient’s skin type, general state of health, and amount of discomfort, as well as the owner’s goals for treatment (e.g. removal of malignancies versus treatment for cosmesis), should be taken into account when pursuing cryosurgery. Additional important considerations should include how many tumors there are, and the lesion size, depth, and location.

Cryosurgery may be an appropriate therapy for tumors that are
- Superficial, small, and noninvasive
- Located in areas where definitive surgical resection cannot not be performed due to anatomical limitations (such as the eyelids, nose, ears, lips, dorsal surfaces of paws, scalp, trunk, and lower parts of the limbs) or due to owner reluctance
- Too numerous for conventional excision
- Present on animals that may carry high anesthetic and post-operative complication risk (e.g. older animals, patients with heart disease or pacemakers, patients on anticoagulation therapy, etc.)

Advantages of cryosurgery
There are several advantages to the use of cryosurgery for appropriate tumors. First, in most cases, no anesthesia is needed. Local analgesics, such as lidocaine, may be administered; however, the cold itself will act as an analgesic. Sedation or anesthesia may rarely be needed for patients who cannot be sufficiently restrained manually, or for larger, deeper lesions where longer freezing times are required. Cryosurgery is also less invasive than sharp surgical excision; it, therefore, carries with it a lower morbidity. In addition, it may help to preserve anatomical structures. Post-operative pain and bleeding are minimized because the cold will temporarily damage the fine nerve terminals, as well as cause contraction and thrombosis of small blood vessels. Histological interpretation is satisfactory following cryosurgery. Finally, cryosurgery can be very efficacious for appropriate tumors. A study in 2008 looked at the clinical efficacy of cryosurgery in 30 dogs with various types of benign and malignant subcutaneous and cutaneous lesions. Of the 30 dogs, only 1 malignant tumor recurred. In a second study, a remission of 83% was reported in cats with squamous cell carcinoma treated with cryosurgery.

Potential complications of cryosurgery
Overall, cryosurgery comes with less morbidity than surgical excision. Most of the transient signs or symptoms that may be seen as “side effects” of cutaneous cryosurgery in actuality represent the normal progression of physiologic processes following the freezing of tissue. Immediately after cryosurgery, you will see erythema and urticaria. This will be quickly followed by edema, which will peak on the third day postoperatively. While steroids may help this edema, they may also delay wound healing; cold compresses may be a better therapeutic option in cases of edema necessitating treatment. After edema, the lesions will produce serous or hemorrhagic exudate, followed by the formation of vesicles (after superficial cryosurgery) or a gelatinous exudate (in deeper treatments). The roof of the bullae is protective, serving as a sterile dressing for the healing of the wounds beneath, and should not be disrupted unless the bullae are causing significant discomfort to the patient. This will eventually be followed by a superficial to deep eschar. It is important
to tell the owners that the lesions will look much worse before they look better, and that there will be a significant amount of exudate before the tumor quite literally falls off.

Complications of cryosurgery can be both transient (immediate and short-term) and permanent. In addition to those mentioned above, immediate effects of cryosurgery can include pain and small amounts of bleeding. Some humans have reported a burning sensation during the procedure which is more pronounced during the thawing process; headaches have also been reported with cryotherapy on head, face, and ear lesions. Tips of digits, the nose, and mucosal surfaces may be particularly sensitive. Most discomfort in humans will diminish within 30 minutes. However, short-term oral or parenteral analgesics, cold-packing, and/or a topical anesthetizing cream may be beneficial in some patients. Deep or acute hemorrhage is rare following cryosurgery, but small amounts of bleeding are possible. If debulking is performed prior to cryosurgery, hemostasis should be obtained before beginning the cryosurgery. Using lubricating jelly on the probe and allowing it to defrost before removing it from the skin will decrease trauma and bleeding. Other immediate complications may include nitrogen gas insufflation of the surrounding tissue, which should dissipate within the first 24 hours after surgery, and syncope, which is potentially related to a vasovagal response. Cold destroys the cells and largely spares stroma, so most injuries to tissues like cartilage and nerves are transient.

Short-term complications of cryosurgery may include infection. Infection, however, is rare due to the destruction of skin flora with freezing and the maintenance of the basement membrane. Infection is most commonly seen in patients with poor wound healing (e.g. chronic steroids, diabetes mellitus) or patients with vascular compromise. In mild cases, antibiotic ointments applied topically may be sufficient, though more severe cases may require systemic antibiotics. A culture to distinguish normal exudate from an infectious process should be performed in cases of suspicion.

Clients should be warned about the likelihood of pigmentary alteration (either hypo- or hyperpigmentation) and alopecia. Permanent nerve damage and cartilage necrosis are more rare complications. Occasionally in humans, nerve damage may result in hyperesthesia rather than loss of function. To avoid these complications, avoid directly freezing tissue deep to the lesion, and avoid prolonged freezing times in areas with thin skin overlying cartilage if possible. Tissue necrosis following the procedure is also uncommon, but may also result in delayed wound healing. Finally, scar formation is an uncommon but possible complication; rarely, retraction scars can occur around the lips or eyes, resulting in ectropion and impaired normal function of anatomical structures.

**When to consider referral**

Cryosurgery is a technique that may be done in the clinic, in most cases without the need for anesthesia. Clinicians with an interest in cryosurgery may feel at ease choosing the appropriate patients and employing the technique to remove superficial, small, and benign lesions. Clinicians who have more experience with the technique may also feel comfortable assessing the amount and area of freezing achieved for malignant, large, and/or deep lesions. However, as with all cancer therapies, referral should be considered for any case in which the clinician does not feel completely comfortable with the type of lesion appropriate for cryotherapy, the technique, and/or the means of assessing intra- and post-procedure success.

**Major points**

- Cryosurgery can be an effective treatment for certain cutaneous and subcutaneous tumors.
- The effects of cryosurgery are not just from the initial act of freezing, but also from the subsequent inflammation, solute redistribution, vascular changes, and immune response to the freezing and thawing.
- Consider cryosurgery if you have a patient that is a poor anesthetic candidate or if the lesions are not readily amenable to surgical excision.
- Following the procedure, warn the clients that it is normal for them to see post-operative edema, erythema, significant exudate, blisters, and eschar formation before the surgical site heals.
- Complications are rare compared to surgical excision, but will most commonly include pigmentary changes and alopecia.
- If you are faced with a malignant, deep, or large lesion, consider referral.

**Table 1. Common cryogens and their freezing temperatures**

<table>
<thead>
<tr>
<th>Cryogen agent</th>
<th>Freezing temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freon 12</td>
<td>–29.8°C</td>
</tr>
<tr>
<td>Freon 22</td>
<td>–40.8°C</td>
</tr>
<tr>
<td>Solid carbon dioxide</td>
<td>–79.0°C</td>
</tr>
<tr>
<td>Liquid nitrogen</td>
<td>–195.8°C</td>
</tr>
</tbody>
</table>

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There are a limited number of tests a veterinary practitioner will be required to perform when presented with a patient with skin disease. For some of these tests, subtle and simple techniques can influence the accuracy of the results.

**Cytology**

Cytology is an invaluable test for a veterinarian to master. Any primary and many secondary lesions such as papules, pustules, crust and exudate can provide helpful information. Staining with Diff-Quik® is usually adequate for most in-house cytologies. A number of methodologies are used to obtain samples, including aspiration, tape preps, swabbing, impression smears, and scraping of surface material. Some of the more important lesions to sample and what to consider include:

- **Pustules:** Neutrophils and possibly eosinophils will be present. Are bacteria present? If so, what is the shape (rod vs. coccoid) and are they intracellular, extracellular or both? Are acantholytic cells present which would be suggestive of pemphigus foliaceus?

- **Nodules:** Fine needle aspiration or multiple insertions of a 20-22ga needle into a nodule can yield cells and help distinguish neoplasia from inflammatory disease. If a homogenous population of cells such as lymphocytes, mast cells etc are seen then biopsies to evaluate for neoplasia are indicated. A mixed inflammatory response could direct the veterinarian to also consider infectious or sterile inflammatory conditions. Any bacterial or deep fungal infection could cause nodule formation. Sterile granuloma, sterile histiocytosis, and sterile panniculitis are examples of conditions which could cause nodule formation without microorganisms.

- **Exudate:** Cytology of exudate can be enlightening regarding potential infectious causes. Exudate is often found in ears, interdigital areas, and the ventral neck region.

- **Crust:** Gentle removal of the crust and sampling the material under the crust can be useful in obtaining information regarding the cause of the crust.

When microorganisms are present, it is helpful to quantify the numbers so that response to therapy can be monitored. We use a 1 through 4 plus system as defined:

- 1+ Organisms are rare to scattered at oil power
- 2+ Many organisms in every field
- 3+ Organisms difficult to count
- 4+ Complete coverage of the field with organisms

**Hair-pluck (trichogram)**

In our practice we will pluck hairs for three reasons. Ectothrix hyphae of dermatophytes may be seen although this requires practice and should not be used alone to diagnose dermatophytosis. Plucking hair and placing in mineral oil can be useful in recovering demodex mites, especially in hard to scrape regions such as interdigital areas. Finally patients with color dilution alopecia will show melanin clumping within the hair shaft resulting in deformation of the medulla and cortex of the hair.

**Skin scrapings**

Skin scrapings are another commonly performed diagnostic test, and are performed to recover mites. Simple techniques to improve chances of recovery of mites start with shaving the area to be scraped. Otherwise the hair will deflect the blade off the skin, resulting in false negative scrapings. Placement of mineral oil on the skin increases the recovery of mites, otherwise the scraped material is to dry to effectively “pick up” mites. When scraping for Demodex, gentle “pinching” of the skin before scraping may force mites in the follicle closer to the surface. Scrape to a depth until capillary bleeding occurs, but avoid vigorous or excessive pressure. When scraping for Sarcoptes there will often be excessive surface crust and debris present on the skin, and subsequently on the slide. Examine this debris carefully. Mites may be more motile after the slide has sat on the microscope for a minute and warmed the contents of the slide. Scraping skin with papules can also be a good area more likely to yield mites. Demodex injai inhabits sebaceous glands in canine skin, so scraping the dorsal trunk where it is most greasy will be necessary to recover this particular strain of Demodex. The numbers of recovered D. injai mites will be lower compared to D. canis populations.

Because of increasing prevalence of methicillin resistant *Staphylococcus* it is advisable to keep spatulas or dull scalpel blades in a cold disinfectant solution such as benzalkonium chloride with an added anti-rust ingredient.
**Dermatophyte diagnostics**

**Ringworm PCR**

The Ringworm (Dermatophyte) RealPCR™ Panel tests for *Microsporum* spp., *Microsporum canis* and *Trichophyton* spp. This real-time PCR test has a greater than 95% sensitivity and 99% specificity and results return within 1–3 working days. You can submit samples by brushing the hair and coat with a toothbrush then submitting the toothbrush in a plastic bag. You can also submit hair with follicles, crusts, nails or skin scraping samples submitted in a red-top tube. This is an excellent test for diagnosing ringworm and for monitoring for fungal clearance. The only possible downside is the chance for false positives in multiple pet households or with environmental contamination.

**Dermatophyte culture**

The most sensitive method of recovering dermatophytes in small animals is to utilize the toothbrush technique. This requires a flat DTM plate be used instead of the small jars which do not have a large enough opening to inoculate the media with a toothbrush. Any suspicious lesions should be brushed vigorously and firmly with a new toothbrush and then the ends of the bristles are gently implanted into the fungal media. In arid environments it helps to then seal the DTM in a plastic bag to reduce drying of the media. Cultures should be looked at daily. The DTM culture, with a pH indicator, will turn red early when a true dermatophyte is present. Color change after several days of fungal growth should be evaluated with caution as saprophytes will cause a color change after carbohydrates in the media are depleted and proteins then metabolized. Dermatophytes will never have dark pigments such as green, brown or black within the colony and if present it should be assumed the growing colony is a saprophyte or contaminant. Microscopic examination of the colony is easily done with clear tape and Lactol Phenol Cotton Blue stain. Plates such as Derm-Duet™ or Sab-Duet™ are available at Hardy Laboratory (www.hardydiagnostics.com).

**Bacterial culture**

Because of increasing incidence of methicillin resistant and multidrug resistant bacterial infections, it is becoming increasingly necessary to perform bacterial culture and sensitivity testing. When performing cultures of superficial pyoderma, it is sufficient to “lance” an intact pustule with a sterile 25 gauge needle and collect the pustule contents on the end of the swab. For deeper infections it may be necessary to obtain tissue for homogenization. In such cases the site is prepared with surgical scrub, and local anesthesia is used. Due to concerns that lidocaine could inhibit bacterial growth, we attempt to perform more of a ring block. A 4-6mm punch is used to obtain the tissue, usually over the site of an intact (non-draining) nodule, plaque, or changes consistent with “bulging” of the skin. The tissue is removed aseptically, and the epidermis could be trimmed if there is concern of surface bacterial contamination. The tissue is then placed in a sterile red top tube, and 1.0 cc of sterile saline is added to prevent desiccation.

If a Mycobacterial infection is suspected, we submit our samples to National Jewish Health in Denver. Many of the microbiology laboratories in the country send samples to this lab if a mycobacterium bacteria is isolated, as they excel in the identification and sensitivity testing for mycobacterium. Further information is available at www.NJlabs.org

**Histopathology**

The vast majority of tissue biopsies obtained can be performed with local anesthesia. Lesions to be biopsied are not prepped or scrubbed in any way except clipping of the hair. Care is taken to not disturb any part of the skin or surface lesions such as crust, pustules etc. The biopsy punch should never be less than 6mm except for biopsies of the planum, foot pad, or pinnae in which case a 4mm punch is used. The punch should only be turned one direction (eg clockwise). To remove the sample, the edge of the SQ tissue is gently grasped with forceps and the base of the tissue punch is clipped with curved iris scissors. Avoid crushing the tissue with the forceps which leads to artifacts. It is not necessary to place punch biopsies on “splints” as has been advocated for wedge samples. Submission to a Dermatopathologist remains one of the most important decisions of the biopsy process, but unfortunately is rarely done.

If a complete signalment, history, sites biopsied, and list of differentials is sent to the pathologist, their ability to provide more definitive answers will be greatly enhanced. Remember the clinician gets to see the entire patient and the pathologist only gets 6mm of tissue!

**Food trials**

Food trials remain one of the more challenging test to perform in practice, partly because of resistance on the part of both the owner and the patient when it comes to compliance. A more complete discussion is provided elsewhere, but at the core, a successful food trial will involve feeding a novel or hydrolyzed protein diet to which the patient has not been exposed to for a minimum of six weeks. Analysis of many of the over the counter foods which claim they contain only one protein and one carbohydrate has revealed contamination with beef, soy, and rice making such diets unable to definitively diagnose a food allergy. Serology and skin testing for food allergies remain inaccurate, with both false positive and false negative reactions being present.
**Allergy testing**

The diagnosis of atopy should be made based on history, clinical presentation and the ruling out of other hypersensitivities such as parasite and food allergy. Once a diagnosis of atopic dermatitis has been made, it may be appropriate to perform allergy testing in order to more clearly define which environmental allergens are contributing to the clinical signs. The only reason to perform serology testing, or to refer a patient for intradermal skin testing, is to follow up with allergen specific immunotherapy (ASIT). Once allergy test results are obtained, these results should always be critically analyzed to insure that the results are consistent with the patients’ pruritus history. This determination must include historical information regarding seasonality. If allergy testing reveals positive reactions to only seasonal pollens in a patient which is pruritic year-round, then something is being missed! Choosing the allergens to be included in the extract is something the veterinarian should personally direct based on the specifics of each individual patient. This is where knowledge of the regional allergens is necessary.
**Fun with Fungus: New Ideas on Managing Ringworm**

Anthea Schick, DVM, DACVD

Dermatology for Animals

Tempe, AZ

**Ringworm basics**

Ringworm, or dermatophytosis, is a fungal infection caused by protein-eating fungi. There are many species of ringworm, but the most commonly cultured fungi are *Microsporum* spp. and *Trichophyton* spp.. These fungi invade the hair shaft and sometimes surface of the skin (the keratin of the upper layers of the skin) and produce large amounts of infective microconidia. Ringworm is much more common in cats than dogs and most often become infected with *Microsporum canis*. Dogs are more likely to become infected with soil and small mammal-associated species like *Microsporum gypseum* and *Trichophyton mentagrophytes*. In our practice, the following dogs are more prone to dermatophytosis: Boston terriers, Yorkshire terriers and Jack Russell terriers.

**Diagnostics**

1. **Wood’s lamp**

A Wood’s lamp is a hand-held device that emits long-wave (between 320 and 400 nm) ultraviolet radiation through a nickel or cobalt glass filter. Electric (plug-in) Wood’s Lamps are generally more consistent than the battery powered ones and I prefer the brand Burton’s, which has two rows of light bulbs with magnifying lens in the center. The magnifying lens allows the clinician to see if individual hairs fluoresce near the base of each hair, which is important in differentiation between positive ringworm fluorescence and false positive from crusts or topical medications. *Microsporum canis* fluorescence is bright apple green and infected hairs glow from the bulb to the tip. Wood’s lamp is only a screening tool for *Microsporum canis* infections, because not all ringworm strains will fluoresce: negative fluorescence does not rule out dermatophytosis. Wood’s lamp examination is cheap and easy to perform and we find it helpful for examining known positive animals (*Microsporum canis*) or animals where *Microsporum canis* is likely. Fungal culture and/or fungal PCR is important to confirm infection. When examining an animal without lesions, focus carefully on the face, ears and paws, as these are commonly infected areas. Wood’s lamp can help identify which hairs to sample for culture/PCR or for direct examination of hairs under the microscope. Wood’s lamp examination can also help monitor response to treatment. With antifungal therapy, there should be fewer Wood’s lamp-positive hairs and the location of fluorescence should progress from the base of the hair to the tip as the hair grows out, moving the infected section of hair upwards.

2. **Directly examination of hairs**

Hairs plucked from near an affected area or ones that fluoresce under the Wood’s lamp can be placed in mineral oil, covered with a cover slip and examined under 10x. Infected hairs may have fungal hyphae within the hair shaft and small round microconidia or spores on the outside of the infected hair. You may see spores ‘exploding’ from the hair shaft and spores surrounding the hair.

A tape prep can be made of a suspicious area and stained with either lactophenol blue or the purple Diff-Quik stain. Ringworm spores will appear round or ovoid and look a bit like non-budding Malassezia. Spores often appear like they have a clear capsule around them.

3. **Fungal culture or dermatophyte culture**

There are many brands of dermatophyte cultures or DTMs (dermatophyte test medium) but the larger surface areas, bi-plate DTM called Derm-Duet II made by Hardy Diagnostics is ideal. The Derm-Duet II has two sections, one section for DTM (Dermatophyte Test Medium) and the other section for RSM (Rapid Sporulation Media). Each plate is individually wrapped, does not require refrigeration for storage and has a shelf life of a year. Cultures can be kept in a plastic storage bin to prevent desiccation and contamination. Ideally, incubation temperature should remain at 75°F to 80°F. To inoculate the plate, you can pluck individual hairs that have or use a new toothbrush or gauze to brush the entire body or a site. Individual hair sampling is best suited for Wood's-lamp-positive hairs or hairs that are grossly abnormal. When plucking hairs, grasp the hair in the direction of growth and tug gently, trying to get the root bulb. Gently press the hair onto the growth medium. For toothbrush or gauze sponge sampling, comb or wipe until hair is clearly visible on the surface or in the bristles or gauze. Be sure to sample near the eyes, in the ears, and between the toes. When inoculating a plate with a toothbrush or gauze, gently stab the bristles or press the gauze over the entire surface of the plate. Plates should be checked daily for fungal culture growth. Ringworm growth will appear white or buff-colored on the DTM (never darkly colored) and will develop a red color change around them as they grow. Most ringworm species will grow and sporulate within 7 to 10 days but *Trichophyton* cultures often take up to 21 days. Plates should be kept for at least 14 days and preferably for 21 days. Collect tape sample from suspicious colonies and stain lactophenol blue stain or the purple Diff-Quik stain then examine on 10x then 40x for macroconidia.

4. **Fungal/Ringworm PCR**

The Ringworm (Dermatophyte) RealPCR™ Panel from Idexx Laboratories is a newish diagnostic tool for diagnosing dermatophytosis in cats and dogs. The panel includes *Microsporum* spp., *Microsporum canis* and *Trichophyton* spp. real-time PCR tests and performs
with greater than 95% sensitivity and 99% specificity. Results are available in 1–3 working days. You can submit samples in a few ways: Use a soft bristle toothbrush to comb the suspect lesion, then submit the toothbrush in a ziplock plastic bag. You can also pluck hair with follicles, lift or remove crusts and/or perform skin scrapings from the active border of suspect lesion, then place in a red-top tube. Nails with nail bed scrapings or clippings can be submitted in sealed fungal envelope or sterile container. As with most PCR tests, this test is very sensitive in detecting any dermatophyte DNA. The only downside I can see with this test is the risk of collecting spores from an animal that has picked up spores from the environment and is not actually infected, leading to a false positive. Using the Wood’s lamp to identify suspicious hairs samples can help decrease the possibility of a false positive. We have recently had several cases of ringworm where the fungal PCR was negative and the DTM was positive. This could be due to differences in sampling, but we are currently performing both ringworm PCR and fungal cultures.

**Treatment**

Treatment involves a multi-pronged approach: topical/and or systemic therapy, environmental management, and in the case of Microsporum canis, assessment for household canine and feline carriers. Recheck with repeat culture should be performed 1-3 weeks after initiation of therapy and every 1-3 weeks thereafter. Treatment should be continued until 2-3 negative cultures are obtained. Treatment duration is variable and may take from 14 days to 6 months. In healthy patients, spontaneous resolution may occur within three months.

**Itraconazole**

- Dogs: 5 mg/kg PO once a day for 7 days, stop for 7 days; repeat pattern 3 times
- Cats: 5 mg/kg PO once a day for 7 days, stop for 7 days; repeat pattern 3 times

Itraconazole, a fungistatic triazole, inhibits the cytochrome P450 enzyme lanosterol 14α-demethylase, which converts lanosterol to ergosterol. Decreases in ergosterol affect fungal cell membrane permeability. Avoid alkalinizing agents (eg, H2-blockers, antacids) with itraconazole. Alanine aminotransferase (ALT) and serum alkaline phosphatase (ALP) levels may rise without liver disease signs, though hepatotoxicity is rare. In cats, the oral solution is preferred to capsules. Generic and compounded itraconazole have not been shown to be bioequivalent to Sporanox®. Generic formulations have shown similar pharmacokinetic data; compounded itraconazole has produced low plasma concentrations in dogs and should be avoided. There is a new formulation of itraconazole recently approved for cats called Itrafungol™. This is less expensive than the Sporanox® formulation and we have been impressed with its efficacy and ease of administration.

**Terbinafine**

- Dogs: 30-35 mg/kg PO once a day
- Cats: 20 mg/kg PO once a day

Terbinafine, an allylamine antifungal agent that inhibits the enzyme squalene epoxidase with a net effect of decreasing ergosterol formation. Terbinafine does not inhibit mammalian CYP and therefore has fewer drug-drug interactions thanazole antifungals. Terbinafine concentrates well in the skin, is well tolerated, and may be used as an alternative when a toxic reaction develops after administration of other antifungal drugs. Some dogs may have heptotoxicity with terbinafine but cats seem to not have similar problems. To my knowledge, there have been no efficacy comparison studies between itraconazole and terbinafine.

**Fluconazole**

- Dogs: 5-10 mg/kg PO twice a day
- Cats: 50 mg/cat PO once a day

Fluconazole is a fungistatic bistriazole that inhibits cytochrome P450-mediated sterol synthesis affecting fungal cell wall function. Food and gastric pH do not alter bioavailability. It is well tolerated orally.

**Topical recommendations (once to twice a week)**

- Lime sulfur (1:16)
- Enilconazole (1:100)
- Accelerated hydrogen peroxide rinse (1:20)
- Climbazole mousse
- Ketoconazole (1%-2%) shampoo
- Miconazole (1%-2%) shampoo

**Environmental control**

If possible, positive animals should be isolated from negative animals, ideally in an easily-cleaned area. Owner should be instructed to clean all non-porous surfaces with 1:10 household bleach or accelerated hydrogen peroxide (Accel®) twice weekly. New studies show that other cleaning agents like Lysol wipes and 409 are effective in decreasing fungal spores. Daily vacuuming should be performed in areas where ringworm positive animals are kept. Swiffer wipes can be used to clean the floors and walls as their electrostatic nature helps attract spores. Any bedding or upholstered items that are difficult to clean should be thrown out-this includes cat tress as they are notoriously difficult to clean. With severe multi-pet infection situations, it might be necessary to clean the ducts and vents in the house.
For patients with *T. mentagrophytes*, reduced exposure to heavily-populated rodent habitats or rodent control is recommended. If rodents are kept as household pets, they may be screened for ringworm carriage using the toothbrush technique. Owners should know that ringworm is zoonotic and told to wash hands their after handling all pets. In the clinic, dermatophyte-positive animals should be isolated from other patients and gloves should be worn during examination. Scrubs or lab coats should be changed prior to examining other patients or a disposable gown can be worn.

Exam rooms should be cleaned with 1:10 bleach or accelerated hydrogen peroxide (Accel®).
Atopy or Atopic dermatitis continues to be one of the most common dermatological disorders afflicting both dogs and cats. At our referral dermatology specialty practice, 75% of our patients have atopic dermatitis as one of the final diagnosis. The problem is so common and severe that many drugs have been utilized in an attempt to offer relief to the suffering patient. The challenge for the clinician is to try and find the right balance between all of the therapy options, their cost, efficacy and safety. The disease continues to generate research, with new therapies being developed.

The International Task Force on Atopic Dermatitis developed guidelines in 2010 for the treatment of atopic dermatitis which involve a multifaceted approach including:

- Treatment of acute flares
- Attempt to ID and avoid all triggers of flare
- Improve skin & coat hygiene
- Treat ongoing pruritus with drug therapy
- Allergen specific immunotherapy should be offered when feasible

The diagnosis of atopic dermatitis is not based on any laboratory or skin test but is based on a combination of signalment, history, clinical signs and the ruling out other causes of inflammatory skin. Obtaining a certain and complete diagnosis for the pruritic patient can be challenging, but is a necessity if efficient and effective care is to be delivered.

When attempting to effectively help a patient with atopic dermatitis it is necessary to understand the pathogenesis of the disease, and teach the client these basic concepts. In dogs, atopic dermatitis is known to be an inherited type 1 hypersensitivity reaction to percutaneously absorbed antigens. Epidermal barrier defects contribute to the pathogenesis. Bacterial and yeast infections provide additional antigens which may exacerbate pruritus.

We try and simplify options with clients and explain there are five groups of options for the treatment of atopic dermatitis. They include supportive therapy, corticosteroids, cyclosporine, oclacitinib (Apoquel®), Cytopoint™ and allergen specific immunotherapy. The point of this lecture is how to minimize the corticosteroids, oclacitinib and cyclosporine (Big Gun Drugs). Allergen specific immunotherapy is covered in more detail in a separate lecture. These options are frequently used in combination in order to obtain synergistic effects, which is an important concept to teach clients. In order to use less of the “big guns” clients must administer more intensive supportive therapy.

Supportive therapy is always a good place to start when treating a “mildly” affected atopic patient and includes antihistamines, essential fatty acids, bathing, restoration of the epidermal barrier, control of secondary infections, and potentially topical anti-inflammatory products. A number of antihistamines have been utilized to control pruritus in dogs. Good clinical trials with placebo controls show the benefits of reducing pruritus ranging from zero to 30%. Many dermatologists will utilize antihistamines as part of the ongoing maintenance control of atopic dermatitis, but recognize their limited value when treating an acute or intense flare. Antihistamines which we currently recommend at our practice include cetirizine, amitryptilline, clemastine, diphenhydramine, and chlorpheniramine. Most are available in generic formulation, and are over the counter, which helps keep the cost low. I usually try 2-3 different antihistamines, but expectations need to be realistic in understanding the value of these drugs may be in their steroid sparing effects. Remind owners to avoid formulas which contain decongestants and pain relief products. At the end of these lecture notes is an antihistamine handout we give to owners.

There are many published reports regarding efficacy of essential fatty acids (EFAs) for the treatment of atopic dermatitis. Unfortunately many of these studies failed to control, or account for the amount of EFAs in the diet, which makes interpretation and comparison of these studies difficult. Most dermatologists support the use of EFAs in the treatment of chronic atopic dermatitis. Despite claims to the contrary, currently it is the position of the Task for on Atopic Dermatitis that there is no evidence of superiority of any particular EFA combination, dosage, ratio or formulation (including enriched diets) to improve skin and coat quality. As with antihistamines, EFAs are not adequate as a single therapy for atopic dermatitis except in mildly affected patients.

Improvement of the epidermal barrier has recently been getting more investigation and implementation. Simply bathing the atopic patients has many benefits including physical removal of antigens, reduction of bacterial and yeast populations, repair of epidermal barrier defects and the anti-pruritic effects of cool water cooling hot inflamed skin. Despite the widespread belief that frequent baths will dry out the skin, most dermatologists believe that a client cannot over bathe an allergic dog. The biggest drawback of frequent baths is the concern of washing away some of the flea control products.

A plethora of OTC and prescription antipruritic shampoos are available with ingredients including oatmeal, corticosteroids, diphenhydramine, pramoxine, lidocaine and coal tar just to name a few. It is the feeling of this author that the higher cost and short-term benefit of these products usually do not justify their use. Instead, at our practice we utilize products with antiseptic and
epidermal restoration effects. Knowledge of any and all infections of the skin should influence the choice of antimicrobial shampoo. Chlorhexidine, tricoslan with ethyl lactate, or benzoyl peroxide are chosen for most allergic patients prone to recurring pyoderma. If the skin is oily, or the infection is deeper than a superficial folliculitis, ethyl lactate or benzoyl peroxide is chosen since they are more potent “degreasers” and have follicle-flushing activity. Shampoos with miconazole or ketoconazole are chosen if the skin is infected only with Malassezia, otherwise a shampoo with multiple ingredients may be needed for a mixed infection of bacteria and yeast. Recently we have utilized a shampoo and spray containing Tris EDTA with a 4% chlorhexidine, particularly when dealing with meticillin resistant Staphylococcal infections of the skin.

Formulations which extend or prolong the antimicrobial effects of the product include “Leave on” lotions/sprays/conditioners/mousses. Also the active ingredient can be formulated into “Spherulites™” or “Liposomes” which adhere to the skin and hair with a slow prolonged release.

The final “goal” of shampoo therapy is to repair or restore the epidermal barrier. Products marketed for this function include L-Rhamnose and phytosphingosine, both of which also contain chlorhexidine. There are also a number of new topical “pour on” products available which attempt to mimic and replace the endogenous lipid barrier of the epidermis. They include ceramides with fatty acids (Virbac), phytosphingosine (Socheval) and EFAs (Dermoscent). Clinical trials are ongoing, but these products make sense if they are in fact able to restore the epidermal barrier, reduce transepidermal water loss, and reduce percutaneous absorption of allergens.

Simple management techniques can be employed to reduce overall allergen load on the skin surface. In addition to frequent baths, the coat can be wiped down on a daily (or more often) basis in an attempt to wipe off allergens. Keeping the hair coat short can reduce the “dust mop” affect of a longer coat. Wearing T-shirts and boots or socks can act as a physical barrier to the allergens.

The advantages of the supportive care options outlined above include safety and benefits, which are seen relatively quickly, although EFA supplementation may require two months before a benefit is seen. Another benefit is that no specific diagnostic testing is required once the diagnosis of atopic dermatitis has been made. There is no cost for monitoring of blood work, or even examinations if OTC products are used. Drawbacks include rather lower efficacy, moderate (or more) cost and they are labor intensive.

The fourth recommendation of the International Task Force is to “treat ongoing pruritus with drug therapy.” We will generally have a lengthy and detailed conversation with the client and explain both short and long-term benefits and side effects of corticosteroids, cyclosporine, oclacitinib (Apoquel®), and Cytopoint™. The pros and cons of corticosteroids are well known to veterinarians and most clients. Cyclosporine can certainly help many pruritic allergic patients, but can be one of the more expensive therapies to maintain except in very small patients. It also commonly causes GI disturbance and cannot be tolerated. There are also many examples of abnormal infections, gingival hyperplasia, and perhaps increased incidence of neoplasia.

One of the newer and exciting medications to treat ongoing pruritus is oclacitinib (Apoquel®), which became commercially available in 2014. Our clinics have used the medication in clinical trial settings since 2009. The advantages of oclacitinib include its rapid onset of efficacy and low incidence of side effects. One of the frustrations of oclacitinib is that for some patients, the efficacy does not last for the full 24 hours after the once daily dosing regimen has been started. We frequently receive calls from both clients and veterinarians about resuming twice daily dosing. We do not recommend twice-daily administration long-term as the chances of immunosuppression are likely to increase. Concerns of increased infection and neoplasia would have to be discussed if twice daily dosing is going to be recommended by a veterinarian. As with all the other options for treating atopic dermatitis, oclacitinib does not adequately control pruritus in all our patients either, so the veterinarian and client are required to consider what additional therapies are needed in addition to oclacitinib to find the best “balance” between drugs, efficacy and safety.

Cytopoint™ is a monoclonal antibody that targets and neutralizes IL-31. IL-31 is an important interleukin that has been shown to be important in contributing to itch in atopic dogs. Cytopoint™ is labeled for use in dogs (NOT IN CATS) given as a SQ injection to block itch. The injection lasts for most dogs for 4-8 weeks. We have also been part of the clinical trials for Cytopoint™. In our experience, it may last even longer but also much shorter, or not at all, in some dogs. We have found Cytopoint™ to be effective in some dogs where other modalities have failed and its safety makes it helpful for dogs that may need other medications to control their allergies.

Even though the final recommendation of the Task Force is “allergy specific immunotherapy (ASIT) should be offered when available”, it seems that with the popularity of drugs such as cyclosporine and now oclacitinib, this option has been cast aside by many practitioners, or only considered if or when these drugs fail. It is the opinion of this author and of the International Task Force on Canine Atopic Dermatitis that this is a mistake. For many atopic patients ASIT can become one of the easier, safer, more cost effective therapies. It can be the only effective therapy that is not a drug, and the only therapy without negative effects on the immune system.

The utilization of sublingual immunotherapy instead of the more traditional injectable immunotherapy has also led to many atopic patients benefiting from immunotherapy more quickly, easily and safely. For ASIT in any form (sublingual or injectable) to be its most efficacious, the clinician will require skills relating to the formulation of allergens, prioritizing positive test results, and teaching the client how to monitor the process.
Primary Secretary Otitis Media
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Primary secretory otitis media (PSOM), also known as "glue ear" or "middle ear effusion" or "otitis media with effusion" (OME) is a disease that affects many Cavalier King Charles spaniels (CKCS). PSOM has also been reported in other breeds, including a Boxer, Dachshund and a Shih Tzu. Clinical signs suggestive of PSOM include deafness, neck scratching, abnormal yawning, otic pruritus, head shaking, head tilt, facial paralysis, or vestibular disturbances.

Pathogenesis
In children OME is more common when there are craniofacial abnormalities like cleft palate present: this is thought to be due to abnormal drainage from the Eustachian tube. The cause of PSOM in dogs is not known but several theories have been posed, including Eustachian tube dysfunction and abnormal quantity or thickness of secretion in the middle ear made by the lining of the tympanic bulla (the mucoperiosteum). To evaluate the possibility of Eustachian tube dysfunction, Hayes et. al. evaluated the relationship between nasopharyngeal conformation and otitis media with effusion (OME) in CKCS. They found an association between OME and the brachycephalic conformation. The CKCS with bilateral OME had a significantly greater thickness of the soft palate and reduced cross-sectional area of the nasopharynx compared to CKCS with unilateral OME and those without OME. The association of these changes in relation to the development of PSOM is not known but these anatomic changes in the nasopharynx may impair auditory tube drainage.

Diagnosis
A bulging pars flaccida (soft part of the ear drum) is often seen in dogs with PSOM, but not all dogs with PSOM have a bulging pars flaccida. A study performed by Lynnette Cole in 2012, compared three diagnostic tests (tympanometry-where an instrument changes the pressure in the ear and measures the eardrum responses to sound at different pressures, pneumotoscopy-where a puff of air is blown into the ear canal and the movement of the tympanum is observed and tympanic bulla ultrasonography) using computed tomography (CT) as the gold standard for the diagnosis of PSOM in CKCS. Sixty CKCS (31 females, 29 males) with clinical signs suggestive of PSOM (e.g. hearing loss, neck scratching, pruritic ears) were enrolled in the study. Forty-three (72%) CKCS had PSOM (30 bilateral, 13 unilateral). A large bulging pars flaccida was identified in only those CKCS with PSOM (specificity of 100%); however, only 21/73 ears with PSOM had a large bulging pars flaccida (sensitivity of 29%). Sensitivities and specificities for tympanometry, pneumotoscopy, and tympanic bulla ultrasonography were (84%, 47%), (75%,79%), (67%, 47%), respectively. Based on the results of this study, a large bulging pars flaccida indicates the presence of PSOM, while a flat pars flaccida may be present in CKCS that have PSOM as well as those that do not. In CKCS with a flat pars flaccida, none of the above diagnostic tests can be recommended as a replacement for a CT scan in the diagnosis of PSOM.

PSOM and Chiari-like malformation (CLM) and syringomyelia
The typical signs of PSOM including: severe head or cervical pain, head tilt, nystagmus, and facial/cervical pruritus are similar to those seen in Chiari-like malformation (CLM) and syringomyelia. Since CKCS are prone to Chiari-like malformation and syringomyelia, Loughin completed a study which looked at the prevalence of PSOM in dogs with CLM. They evaluated sensitivity and specificity of computed tomography (CT) and magnetic resonance (MR) for these tow diseases. MR and CT images from 310 dogs with CLM were evaluated for PSOM and compared with surgical findings (myringotomy). MR results were identical to those of surgical findings. 38.7% of dogs with CLM had PSOM. 32% of dogs were asymptomatic. Clinical signs in this study included: pruritus (31%), hyperpathia (28%) and hearing loss (2.5%). There was a significant difference between the prevalence of PSOM in CKCS (46%) and non CKCS (13%); p<0.0001. Compared with MR, CT had a 62% and 100% sensitivity and specificity for the right bulla and a 72.5% and 97.9% sensitivity and specificity for the left. Based on the findings of the Loughin study, PSOM is a common in dogs with CLM, with CKCS being overrepresented. Their findings suggest that MR is superior to CT for the diagnosis of PSOM in dogs.

Hearing loss evaluation
Brain-stem auditory evoked responses BAER testing in dogs measures hearing by measuring changes in the brain’s electrical activity as it responds to sensory stimuli. The changes are recorded and are referred to as evoked responses. Peripheral hearing loss is categorized as either sensorineural or conductive in origin. Sensorineural hearing loss may be due to injury to the cochlear hair cells in the inner ear (sensory) or to the auditory nerve (neural). The most common form of sensorineural hearing loss in dogs is old-age associated hair cell degeneration. Conductive hearing loss is due to abnormal transmission of sound through the external, middle, and inner ears.
A study by Harcourt-Brown et al., measured BAER responses in dogs with PSOM and found that the middle ear effusion in CKCS with PSOM was associated with a mean conductive hearing loss of between 10 to 33 decibels relative to normal hearing level (dB nHL). Interestingly, none of the owners reported any hearing loss in their CKCS. In the study by Stern-Bertholtz et al. impaired loss was reported in sign of PSOM in 13% of the cases 61 PSOM cases evaluated.

**Treatment**

Typical treatment involves performing a video-otoscopic guided myringotomy into the pars flaccida or the caudalventral quadrant of the pars tensa with subsequent flushing of the mucus out of the bulla. If possible, pre- and post-flush air- and bone-conducted BAER testing is recommended to determine the extent of the hearing loss and whether it is due to PSOM or possibly unrelated. Oral glucocorticoids like prednisone (0.5 to 1 mg/kg q 24h for 10-14 days) help with post video-otoscopic inflammation. If concerned, a broad spectrum systemic antibiotic can be prescribed. Clinical signs are usually improved after myringotomy but, eventually, the middle ear will refill with mucus and require another procedure. Some veterinarians have used oral over-the-counter N acetyl cysteine (600 mg q 24h), which may help to extend the symptom-free time. Unfortunately, no prospective studies have been performed to determine the efficacy of N acetyl cysteine in the management of PSOM.

In people with chronic OME, tympanostomy tubes have been used to provide drainage. Two veterinary studies have been published using tympanostomy tubes to treat CKCS with PSOM. Dogs in both studies had relief of clinical signs for a maximum of 8 months when tubes were placed. Some problems were plugging of the tubes and tubes migrating from their placement. Tympanostomy tubes could be an alternative to repeated myringotomies for treatment of PSOM, but requires specialized training (at the level of a human Ear, Nose and Throat surgeon) and special equipment like an operating microscope would likely be needed.
Unlocking the Mysteries of the Ear:
Diagnosing Otitis and Dealing with Chronic Otitis
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Pathogenesis
Canine otitis externa affects approximately 10-20% of canine population and is one of the most common diagnoses after dental disease in general veterinary practice. There is evidence that the prevalence of canine otitis externa is on the rise. A 2011 Banfield Pet Hospital’s State of Pet Health Report evaluated data from 770 hospitals and found that the diagnosis of canine otitis has increased by 9.4% since 2006. Since canine otitis externa can be one of the most frustrating diseases for pet owners, having a thorough and aggressive approach to its diagnosis and treatment is essential.

When confronted with a case of chronic or recalcitrant otitis in a dog, I first attempt to discuss three fundamental concepts with the pet owner. The first point they must understand is that otitis externa is really just a clinical sign, not a final diagnosis. The second is that normal dogs do not get otitis. The third point is that bacteria and yeast are not the cause of otitis but the result of otitis.

Why normal dogs do not get ear infections: Ears have a way of cleaning themselves; this process is largely due to epithelial migration (EM). EM in the ear begins at the tympanic membrane. As epithelial cells divide, they migrate up and out and in a slight spiral pattern, carrying cerumen and trapped debris and organisms out of the ear. When there is damage to the tympanic membrane or the ear canal epithelium, EM is the process of repair. A recent study evaluated the speed of EM and found that the epithelial cells travel about 100 to 200 μm/day.

Why bacteria are not the cause of otitis: The ear is also normally colonized by a variety of organisms including Staphylococcus spp., Streptococcus spp., Corynebacterium and Malassezia spp. These organisms live in harmony with a normal ear canal. With inflammation, these resident organisms and other opportunistic bacteria like Pseudomonas spp. (a ubiquitous organism often found in water and able to colonize plumbing fixtures) can overgrow and cause infection.

Why otitis externa is not a diagnosis: A commonly used conceptual framework for understanding canine otitis externa uses the terms predisposing, primary and perpetuating factors. A combination of these factors is needed to produce clinical disease.

Predisposing factors
Predisposing factors are factors that increase the risk of development of otitis externa. For example, conformation (narrow ear canals like in the Chinese Shar-Pei), environment/lifestyle (humid climates, trauma from ear plucking, excessive swimming, over exuberant ear cleaning).

Primary factors
Primary factors begin the condition, For example, parasites (Otodectes, Demodex, ear ticks), foreign bodies (grass awns), tumors (benign-polyps and adenomas, neoplastic-adenocarcinoma, squamous cell carcinoma), hypersensitivity disorders (atopy, adverse food reactions, drug/contact reactions), keratinization disorders, glandular disorders (excessive cerumen/sebum accumulation, sebaceous adenitis), immune-related (hypothyroid) and auto-immune (pemphigus complex).

Perpetuating factors
Perpetuating factors prevent the resolution of otitis. For example, organism overgrowth (bacteria, yeast), loss of epithelial migration, chronic changes in the ear (epidermal/glandular hyperplasia, stenosis, fibrosis, ossification, otitis media).

Failure to identify and address these factors likely will result in ongoing otitis and possible end-stage otitis. In end-stage otitis, inflammation and ear canal hyperplasia leads to stenosis and thickening of the ear canal wall, often with complete closure of the ear canal. Fibrosis of the canal and ossification of the auricular and annular cartilages is the final step in the end-stage ear. At this point, medical therapy cannot reverse these changes, and total ear canal ablation with lateral bull osteotomy (TECA-LBO) is often recommended.

Diagnostic approach
Here are some steps and tips to treat canine otitis externa and prevent the progression to end-stage otitis. At first exam, a thorough history should be taken. For example, we must know age of onset, unilateral vs. bilateral, seasonal patterns, additional dermatologic signs, current and previous diet, behavior and environment, general health, neurologic signs observed, other pets affected, and what treatments are currently being used and how often and with what success.

Next, a thorough clinical exam (both physical and focused dermatologic exam) should be performed. I begin by palpating the external ear canal to assess pliability and pain. I palpate both mandibular lymph nodes since they often give hints if there is otitis media or more severe inflammation is present in one ear. Check for neurologic deficits that might indicate otitis media. Lastly, I open the mouth widely to assess for discomfort at the temporomandibular joint, which also may indicate otitis media.
Ear anatomy

The external ear is made of two pieces of cartilage that fit together forming an irregular L-shaped bend in the canal. The annular cartilage makes up the horizontal canal and attaches to the skull. The auricular cartilage attaches to the annular cartilage and makes up the vertical part of the ear canal. It becomes funnel shaped as it travels distally and then finally expands to form the pinna. The vertical canal travels vertically and slightly rostrally before turning medially and forming the horizontal canal. At the junction of the vertical and horizontal canal, there is a prominent ridge (called either the dorsal ridge or Noxon’s ridge). When the ear is in normal position, this ridge blocks the passage of an otoscope.

The following quote from a classic anatomy text dryly sums up this significant anatomical problem: ‘Unfortunately, its external acoustic meatus is curved, making the passage of the straight otoscope for the examination of the proximal part of the meatus and eardrum difficult’ From Dyce, Textbook of Veterinary Anatomy.

There is a variable amount of hair in the ear canals of dogs. Some breeds, like poodles, will have abundant hair extending all the way into the horizontal canal. In the proximal horizontal canal, just at the level of the entrance of the cartilaginous external acoustic meatus are a small number of few fine hairs and often a small amount of cerumen. These hairs are a helpful landmark that indicates you are close to the tympanic membrane.

The tympanic membrane or ear drum is made of two parts: the pars tensa and the pars flaccida. The pars tensa is the taught, usually transparent part of the tympanum, which is the most obvious part of the ear drum to observe. The manubrium of the malleus attaches to the pars tensa and slightly pulls the tissue of the pars tensa proximally into the middle ear. The attachment of the malleus to the tympanum is called the stria mallearis, which has a slight C-shaped curve, which points toward the nose. From the stria mallearis, small tension lines or striations can be seen as well as blood vessels that supply the ear drum. At the tip of the stria mallearis is the umbo. The umbo is an important landmark, as it is a source of epithelial migration and healing for the tympanum. Care should be taken to avoid damaging the umbo when flushing ears or performing a video-otoscopy. The pars tensa should be clear enough to visualize a bony ridge in the middle ear, which looks like a dorso/ventral white line running. The pars flaccid, or soft part of the tympanum, is dorsal and caudal to the pars tensa and is sometimes blends into the epithelium of the horizontal canal. In other dogs, it is more obvious and looks like a pink, smooth, ‘puffy’ bulge. Occasionally, dogs will have such prominent pars flaccidas, they can be mistaken for masses or polyps.

Middle ear

The tympanic cavity consists of a small epitympanic recess and a large ventral bulla. The tympanic bulla proper is adjacent or behind to the tympanic membrane. In the dog, there is an incomplete bony septum or tympanic bulla ridge (also called Rosychuk’s Ridge). On the medial wall of the tympanic cavity, there is a bony promontory, which houses the cochlea. The cochlear (round) window is located on the caudolateral portion of the promontory. When flushing the middle ear, avoid this promontory or the round window, to avoid damaging the inner ear. The middle ear cavity of the cat is completely divided by a bony septum into two separate tympanic cavities. The auditory tube is a short canal that extends from the nasopharynx to the rostral portion of the tympanic cavity proper.

The three auditory ossicles, the malleus, incus and stapes, are the bones that transmit and amplify air vibrations from the tympanic membrane to the inner ear.

Otic exam

One of the challenges of assessing otitis externa is the difficulty of performing a good otic examination. In my opinion, few practitioners (including myself!) were taught to properly examine an ear while in veterinary school. In fact, most interns and even some visiting residents that I teach need help with their ear exams. There are two kinds of heads for hand-held otoscopes available in most clinics, the operating head and the diagnostic head. The diagnostic head has a large lens that can completely cover the otoscope head as well as a small port to attach a tube for pneumotympanoscopy. The operating head has a small lens that can be moved and instruments can be passed into the ear canal while still visualizing the ear. I recommend experimenting with both heads if they are available. In my opinion, the operating head is superior for most ear exams as the focal length of the lens is better suited for visualizing the tympanic membranes.

Once you have chosen your otoscope type, you are ready for your ear exam. Understanding the normal anatomy of the canine ear is essential in performing a good ear exam. The dog should be around chest height on a table with a technician holding the muzzle of the dog for restraint (not with their arm around the neck-since this impedes movement of the ear canal necessary for a good ear exam). The otoscope should be placed in the intertragic notch while the canal is then visualized. The most challenging part of the ear exam is passing the dorsal ridge, which lies before the junction of the vertical and horizontal canal. The dorsal ridge is what most people run into when dogs seem painful during examination. To avoid this, pull the pinna out (laterally) and slightly down (ventrally) while simultaneously ‘diving’ underneath the dorsal ridge while you advance into the horizontal canal. I find that performing a good ear exam requires more movement and body repositioning than one would think. A good way to practice your ear exam is on sedated or anesthetized patients. After 5-10 ears, you get the ‘pull and dive’ move down. Once in the canal, assess for evidence of ulceration,
extent of hyperplasia or exudate/debris. Once in the horizontal canal, advance toward the tympanic membrane. In order to see all parts of the tympanic (pars tensa, pars flaccida, and the stria mallearis) as well as the ‘corner pocket’-a little recess rostral to the tympanic where foreign bodies sometimes hide-you must move your head quite a bit, much like trying to visualize a room through a keyhole.

Otic cytology
After your ear exam, take samples for cytology. Samples should be taken from the vertical and horizontal canal junction using a cotton-tipped applicator. To remember which sample came from which ear, I break the wooden part of the applicator with the left ear sample. I smear the sample from the left ear near the frosted part of a glass slide and the right at the other end. Heat fixing is not important. After a quick stain with Diff-Quik, examine the slide under oil immersion (x100). The number of organisms and/or inflammatory cells should be determined at each visit.

Record organisms by their size, shape and number. For bacteria, a scale of 1+ to 4+ is commonly used, with 1+ reflecting a few bacteria (easy to count per filed) and 4+ reflecting a large number (impossible to count, almost a uniform layer of organisms per field). As Malassezia is larger and easier to count, record an approximate average of yeast per high powered filed (hpf), for example, 1-5/hpf, 5-10/hpf, 10-20/hpf or TNTC (too numerous to count-TNTC). More than 4 Malassezia and 10 bacteria per oil immersion (x100) are abnormal in dogs. The presence of organisms is not synonymous does not mean infection. Rare bacteria or yeast noted within the cerumen or on epithelial cells, with no inflammatory cells indicates colonization. Inflammatory cells indicate more significant infection and any organisms engulfed by white blood cells are clear indication of infection.

To culture or not to culture
The results of bacterial culture and sensitivity and minimum inhibitory concentration (MIC) measurement may be used to determine the best systemic antibiotic choice. There is some evidence that systemic antibiotic therapy is not helpful in the treatment of otitis externa, and may contribute to colonization by resistant organisms. Since most cases of otitis externa will respond to topical therapy (as long as the underlying disease/problem is addressed), I rarely perform a bacterial culture. In my opinion, you will almost always choose the correct topical antimicrobial by making and empiric choice based on your cytologic findings. Even in a case of ‘resistant’ Pseudomonas spp., if you use high enough concentrations and large volumes of topical antibiotics (enrofloxacin for example), you will largely overcome resistance mechanisms. Remember that MICs on culture and sensitivity panels reflect the concentration of antibiotic achievable in the serum after systemic administration of the antibiotic. With topical therapy, the concentrations of the antimicrobial with far exceed drug concentration achievable in the blood. When you suspect otitis media, however, performing a culture and sensitivity is valuable in aiding systemic antibiotic therapy since the organisms present in otitis externa and those present in otitis media are often different. Obtaining an uncontaminated sample of the middle ear is best done through video-otoscopy.

Diagnostic imaging
Radiology: This is relatively easy diagnostic since can be done in-house. The most commonly uses views are used when assessing ear disease with radiographs: dorsoventral-allows comparison of bullae and petrous temporal bones between sides, rostocaudal open mouth- allows comparison of bullae and external ear canal between sides and lateral oblique-allows bulla evaluation without interference of other bony structures. Non-fancy radiographs can be taken easily and quickly to evaluate whether ossification of the external ear canal is present, which would indicate an ‘end-stage ear’. Radiographs are helpful if obvious middle ear disease or present but studies have shown that normal radiographs do not rule out middle ear disease.

Computed tomography (CT): CT allows more precise evaluation of bony structures in the middle and inner ear than MRI. The tympanic bulla and any bony osteolysis/proliferation can be readily seen with CT as can the ossicles. The sensitivity of CT for detection of otitis media has been reported to be around 83%.

Magnetic resonance imaging (MRI): allows for more precise evaluation of soft-tissue structures than CT and radiographs and should be used when there is concern of soft tissue changes/masses.

Video otoscopy
This procedure is both a diagnostic tool and therapeutic tool. It can be used for deep and precise cleaning of the ear canals and middle ear cavity as well as to evaluate the ear canal middle ear cavity. Foreign bodies can be found easily and removed while minimizing damage to the tympanic membrane. Polyps and masses can often be removed or at least debulked and submitted for histopathology. VO also allows collection of specimens for bacterial culture and sensitivity from the middle ear cavity and application of medications directly into the bulla. To maximize access to the ear canal and to decrease debris, I recommend treating the patient for at least 10-14 days with 1-2mg/kg prednisolone orally once daily. I will often prescribe tramadol to help with pain before the procedure and to make it easier for the owner to treat the ear. After several days of glucocorticoids and tramadol, I will have the owners begin flushing the ears (no more than twice weekly) and applying topical ear medications that contain glucocorticoids (twice daily for one week then daily until the procedure). At the two week recheck, if the ear canals are very stenotic and fail to open up with such aggressive oral and topical anti-inflammatory therapy, medical therapy is unlikely to fully resolve the otitis and surgery may be necessary.
VO Procedure: Obtain samples of the otic exudates from the junction of the vertical and horizontal canal for culture and sensitivity. These cultures can then be set aside for possible submission. I rarely submit culture from otic exudate in cases of otitis externa, but once you start flushing the ear, much exudate will be lost and culture results possibly altered by flushing agents. If there is not too much exudates or mass(es) present and you suspect otitis media, collect samples of exudates from the middle ear for culture and sensitivity. To collect samples from the middle ear cavity introduce a sterile 3.5 Fr x 5-1/2" Tom cat catheter with a 2ml syringe filled with 1-2ml of sterile saline through the working port of the video-otoscope into the middle ear cavity. Flush the fluid into the cavity and aspirate for culture and sensitivity. If the tympanic membrane is intact but middle ear disease is present or suspected, you can perform a myringotomy. I use a sharpened Tom cat catheter to push through the tympanic membrane at the caudoventral part of the pars tensa at 5 to 7 o’clock. It is difficult to rupture a normal tympanum but diseased tympanums will tear with little pressure.

I then take pictures of the canal at mid-vertical canal, just beyond the junction and at the level of the tympanum before placing any flushing agents into the canal. These pictures are helpful to show the owner ‘before and after’ pics. I use a cerulytic agent to fill the canal and then massage the canal for several minutes while pulling the pinna to take the L-shape out of the ear canal. This will allow material to more easily be removed. Warm saline is the used to flush the canal with a Tom cat catheter and 12 cc syringes. There are flushing/suction machines available as well but I like the force that the 12cc/Tom cat combination creates. If there is abundant debris or inspissated material, I will aspirate the saline out and repeat the cerulytic to try to ‘break up’ the debris. Repeat flushing until the canal is clean. I often find a biofilm of sorts on the pars tensa of the tympanum in cases of chronic otitis, which needs to be removed by close-up flushing. This material often peels off like old wallpaper being removed.

If there is a tear in the tympanum, flush the middle ear cavity multiple times with saline. After flushing, aspirate all saline and instill ½ cc each of large animal enrofloxacin (100mg/ml) and dexamethasone SP into the middle ear. Warn the owner that temporary or permanent (very rare) vestibular syndrome, facial nerve paralysis and Horner syndrome can occur post-myringotomy or even with an intact tympanum in a cat. After the procedure, I continue topical and systemic steroids after to reduce inflammation help the ear canal heal itself.

Therapy

Ear cleaning

Start all treatment(s) with a clean ear. Flushing the ear canal is necessary to remove cerumen and debris to allow topical products to reach the canal epithelium. Purulent exudate and inflammatory mediators can inactivate some medications. In cases of severe otitis, where erosions/ulcerations are present, I recommend 4 days of systemic glucocorticoids to reduce inflammation before having the owners clean or medicate the ears.

Over the years I have discovered (often the hard way) that most owners have no idea how to properly clean their dog’s ears. Even owners who have had to manage ear infections for years rarely clean ears correctly. I have ear models in each exam room, which I use to show owners the anatomy of the dog’s ear. Demonstrate ear cleaning in exam room with the owner. If I suspect that they are not cleaning correctly, I sometimes have the owners show me how they are flushing. I recommend that they hold on to the pinna and fill the ear canal with cleaner. While still holding onto the pinna, they should gently pull the ear outwards and feel the ear canal starting from the outer ear down to the base. Once they have felt where the ear attaches to the skull, they should massage the horizontal canal so that a ‘squish squish’ sound is made. While still holding the pinna and continuing to pull laterally, they should use cotton balls or gauze to wipe out the excess fluid and debris. I instruct them to repeat this process until the cotton balls come out clean (or if any blood is seen). Once they are done cleaning, they can let the pinna go and the dog will shake any excess fluid out (and sometimes more debris). Here is a link to a video for owners showing how to clean a dog’s ear:
http://www.youtube.com/watch?v=brCwQftfJ0o&feature=plcp

For more severe otitis or when otitis media is suspected, an ear flush under anesthesia is recommended. The most thorough and accurate was to perform a flush, which also allows precise myringotomy and mass removal/biopsy is a video otoscopic flush. After obtaining samples for cytology and/or culture, I instill a cerumenolytic agent and massage for 5 minutes. Warm saline is then used to flush the ear and curettes or graspers can be used to mechanically remove large chunks of debris. I will often spend 30 minutes per ear in order to adequately clean a chronically infected ear. Another benefit of a video-otoscope is that it allows forceful and directed yet precise flushing of the tympanic membrane. In my experience, chronic purulent otitis will leave a ‘biofilm’ of sorts adhered to the pars tensa of the tympanum. This film is somewhat transparent, making it difficult to assess with a regular otoscope. After flushing the majority of the exudate from the ear, I will place my flushing catheter directly against the pars tensa and flush, often observing peels of adherent exudate dislodging from the pars tensa. After flushing and aspirating the excess fluid, I instill 0.5 ml each of 100 mg/ml enrofloxacin and dexamethasone SP.

Topical medications

As mentioned above, choose topical antimicrobials based on cytology findings. When coccoid bacteria are seen, you are most likely dealing with Staphylococcus pseudointermedius or schleiferi or possibly Streptococcus spp. When rod shaped bacteria are seen, Pseudomonas aeruginosa is the most likely culprit.
Many veterinary products are available for canine otitis externa containing combinations of antibiotics such as neomycin, gentamicin, polymixin B, and enrofloxacin with anti-fungal agents and/or corticosteroids. Common treatment protocols include twice-daily treatment for the first week, then once daily for the second week pending a re-evaluation. With any topical ear medication, make sure the patient is receiving enough volume to be effective. Anywhere from 0.5 ml to 1 ml (10 to 20 drops) is usually enough to treat most canine ears.

**Glucocorticoids**

Virtually all cases of canine otitis externa should have the benefit of glucocorticoids. Most organisms thrive in an inflamed environment, reducing the inflammation alone is sometimes enough to allow the ear canals to 'self-cure'. Glucocorticoids reduce cytokine production, resulting in decreased inflammation, pruritus and pain. Glucocorticoids also decrease the production of cerumen and sebum, as well as secretions from the mucoperiosteum lining the middle ear. There are many topical corticosteroids available, including fluocinolone, betamethasone and dexamethasone. Some dermatologists recommend using topical steroids alone (without additional medications like antimicrobials).

Moderate to severe cases of otitis externa usually benefit from systemic glucocorticoids at relatively high doses (prednisone/prednisolone/methylprednisolone orally at 1-2 mg/kg/day). Glucocorticoids have also been shown to aid in the elimination of resistant Pseudomonas strains through changes in the microclimate that no longer favor the growth of the bacteria.

**Antifungal therapy**

Many of the topical antimicrobial combination products containing an antifungal should be effective for *Malassezia* otitis. Since there is little concern about the development of resistance in *Malassezia*, I will sometimes use oral antifungals, such as ketoconazole 5 mg/kg q 24h, itraconazole 5 mg/kg q 24h, or fluconazole 5-10 mg q 24h for 2-4 weeks for recurrent *Malassezia* otitis.

**How I treat**

With a typical severe painful purulent otitis externa, I prescribe a gentle pH neutral ear flush and a concentrated enrofloxacin/dexamethasone combination. I prescribe tramadol for pain and recommend that the owner start systemic glucocorticoids at about 1-2 mg/kg per day for 10-14 days. After four days of systemic glucocorticoids and pain medication, the owners are allowed to clean and medicate the ears. I have the owners clean the ears no more than twice weekly and use the topical medication twice daily for the first week then once daily. I instruct the owners not to apply either ear wash or medications for 2 days before a recheck examination so that I can more easily assess the tympanum and deep ear canal. At recheck (in 10-14 days), most cases will be improved greatly allowing the systemic glucocorticoids to be tapered. I perform cytology at initial examination and at all re-evaluations. If the primary cause of the otitis has not been evaluated and treated, tapering the glucocorticoids will simply lead to an eventual flare in otitis. Therefore, the MOST important part to successful treatment of canine otitis externa is finding the cause.

Depending on the details of each case, this can mean checking lab work +/- thyroid levels, performing elimination diet trials, intradermal allergy testing and immunotherapy, etc..

**References**

Atopy

Allergy shots (immunotherapy or desensitization) have been one of the safest, non-drug methods to treat allergies in people and animals for many years. It also remains one of the more challenging aspects of dermatology to master. The success of immunotherapy depends on the accuracy of the test used to identify allergens, the formulation of the allergen and the experience of the practitioner.

Allergen specific immunotherapy is most definitely not a “one size fits all” program. If a veterinarian wants to become proficient at administering immunotherapy, she or he should first become familiar with the regional pollen producing plants, when they bloom, how long they bloom, and how prevalent the plant (and allergen) is in the area. An awareness of the prevalence of indoor, potentially year round allergens, such as house and storage mites, mold spores, animal and human dander and insect particles is also necessary. This requires advanced training beyond what can be learned in veterinary school. The first critical step in achieving success with allergy shots is determining accurately and completely what the patient is allergic to. Some veterinarians, clients, and drug companies spend a lot of time discussing the pros and cons of different types of allergy testing. We utilize intradermal skin testing almost exclusively pinpointing the allergic triggers. We find we get the most accurate results from intradermal testing. This also allows us to customize the list for which we are testing based on specific location, not just region. Our current skin test panel includes 70 different allergens and we are constantly modifying what we test for and strength of the testing allergen based on current research. We feel that the more we are proactive about what we test for and how we adjust our patient’s immunotherapy, the better our results are.

When blood (serology) testing is performed, the testing is performed by various regions. Does it really make sense to lump Southern Arizona in the same region as northern Montana when considering what allergens to test for? Intradermal allergy testing is expensive to set up and maintain, and requires practice and skill interpreting results and is therefore mostly performed only in a specialty setting. If intradermal testing is not available, then serology testing must be utilized. It should be emphasized that the only reason to perform any type of allergy (blood or skin) testing is to follow up with immunotherapy.

In the past the only way to desensitize a patient was to give the allergen by injection. Now we also have the option of sublingual. Once allergy test results are obtained, these results should always be critically analyzed to insure that the results are consistent with the patients’ itch history. This determination should include historical information regarding what seasons of the year are better or worse. If you have an allergic dog, cat or horse, we always want the client to pay close attention to these details since it can make a difference on our allergen selection. If allergy testing reveals positive reactions only to seasonal pollens in a patient who is pruritic year-round, then something is being missed. There is a saying in medicine that goes “treat the patient, not the lab results”. This certainly applies to desensitization and the selection of allergen but this is where knowledge of the regional allergens is necessary. For the outdoor working dog that is pruritic only in the summer and fall, then positive reactions to grasses and weeds should be present, and they need to be emphasized or prioritized when formulating the extract. For the indoor Chihuahua which sleeps under the covers at night and who is itchy year round, then indoor allergens such as dander, mold spores, house dust and house mites need a higher priority in the extract recipe.

The volume, concentration, and frequency of the allergen injections are additional variables which will affect the success of the immunotherapy program. We have utilized a “rush immunotherapy protocol” in over 6,000 patients over 25 years. With this schedule, patients receive beneficial levels of allergens within two weeks. We find patients respond more quickly to this program, which can be important for the suffering patient. Yet each patient will respond differently to immunotherapy so there is no “set in stone” protocol. Determining the most effective volume and frequency of injections requires close observations by the owners and the ability of the clinician to make proper adjustments of the protocol. If you have a patient on a desensitization program, we always like to know about any consistent patterns.

For many allergic patients, immunotherapy is one of the more safe, cost effective and medically effective options for managing their disease. In general it is easy for most owners to administer. It is an excellent choice in large and or young patients where the long term lower maintenance costs are best realized. It is also an excellent choice for the non-seasonal patient where treatment with corticosteroids or cyclosporin on a long-term basis would have medical or financial drawbacks. Consequently it is not as good a choice for the geriatric patient, or patient with short-term seasonal disease. Immunotherapy does not lend itself to starting and stopping (using as needed) unlike the other medical options.
**Otitis-video otoscopy**

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**Staphylococcal pyoderma**

Antimicrobial resistance is becoming a problem in veterinary medicine as it has become in human medicine. Methicillin-resistant S. pseudintermedius (MRSP) carries the mecA gene, which encodes for a mutant penicillin binding protein, which prevents binding of beta-lactam antibiotics. The recently formed Working Group on Antimicrobial Guidelines by the International Society for Companion Animal Infectious Disease (ISCAID) has come up with some guidelines about bacterial culture and antimicrobial susceptibility testing. They recommend bacterial culture be performed in the following cases: if there is a poor response to two weeks of appropriate systemic antimicrobial therapy, if there is emergence of new lesions two weeks or more after the initiation of such therapy, if there are residual lesions after six weeks of therapy combined with cytology demonstrating infection with coccoid bacteria or when cytology demonstrates intracellular bacterial rods.

Samples for culture should be taken from pustules if possible or taken from beneath crusts, or from papules or epidermal collarettes. First line drugs which for Staph pyoderma include clindamycin, first generation cephalosporins, potentiated sulphonamides, erythromycin, lincomycin and doxycycline. Second line drugs can be used when first line drugs are not effective (cefovecin and cefpodoxime, fluoroquinolones, chloramphenicol and rifampin). In my opinion, third tier drugs, including vancomycin and linezolid, should not be used in veterinary medicine and saved for human use.

**Erythema multiforme/Toxic epidermal necrolysis**

Erythema multiforme (EM) is caused by a host specific cell mediated hypersensitivity reaction induced by various antigens. The most common cause of EM in people is herpes virus. In dogs EM can be triggered by drugs, chemicals, infections, neoplasia and food allergy. Toxic epidermal necrosis (TEN) is usually caused by a drug reaction and occasionally linked to infection or neoplasia. In both EM and TEN, altered keratinocytes become targets of an aberrant immune response, resulting in keratinocyte apoptosis/cell death.
Clinical presentation EM: Erythematous macules to slightly raised papules which spread peripherally and clear centrally. Urticarial plaques, vesicles, bullae, ulcers can occur. Lesions most commonly affect ventrum, mucocutaneous junctions, pinnae and footpads. EM can sometimes cause generalized scaling/crusting, erythema and alopecia. Oral ulcerations may be present in some cases of EM. The affected dogs may be painful and rarely pruritic. Dogs with a severe case of EM may be febrile and systemically ill. Clinical presentation TEN: TEN is a life threatening, acute onset disease. Patients will present with pyrexia, anorexia, lethargy, depression. TEN skin lesions appear as multifocal to generalized erythematous macules or patches involving skin and multiple mucosal surfaces. There are often painful vesicles, bullae, necrosis and ulcers. The oral mucosa, mucocutaneous junctions and footpads are often affected. There may be a positive Nikolsky sign.

Treatment of EM: Identify and treat underlying cause. Discontinue all suspect drugs administered in 2-4 weeks before disease onset. Look for infections and neoplasia.

Mild cases may spontaneously resolve within 2-4 weeks. Immunosuppressive treatment may be needed for severe or refractory cases (prednisone 1-2 mg/kg po q 12-24, cyclosporine 5-10 mg/kg po q 24, azathioprine 50mg/m2). Pentoxifylline 10-30 mg/kg q 8-12 may be helpful.

Severe cases may require supportive therapy and some cases may need IVIG. Treatment of TEN: Correct underlying cause. The sequelae and prognosis similar to second degree burns. Provide symptomatic and supportive care. Glucocorticoid use is controversial. Plasmapheresis and immunoglobulin 0.5-1.5 mg/kg IVIG once or twice, 24 hours apart may help but there is still a guarded to poor prognosis for dogs with TEN.

Dorsal thermal necrosis

Most burns in veterinary patients are caused by heat from fires, hot liquids, heating pads, driers and hot metals like wood stoves. Of these, most of us are familiar with the dramatic and often extensive burns caused by heating pads, which can cause full thickness burns of large areas of the skin, often on the dorsum. Sustained exposure to sunlight combined with high ambient temperatures can cause burns that are very similar in appearance to heating pad burns. This type of burn has been reported in dogs and has been called ‘dorsal thermal necrosis’. As opposed to most other types of sun damage, which tend to affect light-colored animals or areas of sparse hair, dark haired dogs or those with patches of dark hair are affected. Black skin absorbs approximately 45% more solar radiation than white skin, so it is likely that these dogs are absorbing more damaging UV and visible radiation. Many cases of dorsal thermal necrosis occur in dogs that have been accidentally left outside at high temperatures or in dogs that are taken on long walks/hikes during the summer. It is probable that these dogs could feel the heat and likely pain during the sun exposure but were unable or not allowed to move away from the heat.

Clinical Features: There is often a delay of several days to a week or more from the time of injury to presentation. Some dogs are presented to veterinarians immediately after the heat exposure for heat related problems like fever, lethargy, and dehydration. They have no overt clinical cutaneous lesions and are often treated with supportive care. The owners of some dogs presented to our clinic for dorsal thermal necrosis report that their dogs seemed to resent petting of their backs soon after exposure with increasing discomfort with time. Cutaneous signs include well-demarcated erythema to erosion and ulceration with deeper burns. The affected area is irregular but affecting the dorsal midline although one of our cases was more affected on one side presumably due to the angle of the sun during a long summer hike. In full-thickness burns, eschar will form and the skin will slough. Secondary infection, with purulent exudate and crust formation is usually present, especially with full-thickness burns.

Treatment: Control of secondary infections, pain management and wound care are essential in cases of dorsal thermal necrosis. Surgical removal of affected skin (once the affected area has declared itself) can speed healing. In cases with large surface area affected, sometimes multiple surgeries are required involving skin grafts and stretching techniques. For smaller areas or for owners where surgery is not an option, wound management with frequent rechecks can lead to a good outcome.

Vasculitis

Vasculitis is inflammation of blood vessels resulting in compromise of blood supply to affected areas. The inflammation is due to overstimulation of the immune system by many possible causes including infections (bacterial, viral, fungal, or tick-borne diseases), drug or vaccine reactions, tumors, and autoimmune diseases (especially systemic lupus). In many cases, an underlying cause cannot be determined. Vasculitis is uncommon in dogs and rare in cats. Any age, breed, or gender can be affected, although some breeds may be over-represented such as Jack Russell Terriers and (in cases of vaccine-induced lesions) small silky coated breeds such as poodles and yorkies.

Clinical Features: Symptoms include bruising, localized areas of necrotic (dead) skin and skin ulcers especially in areas such as the ear pinnae, lips, mouth, paws, tail, and scrotum. In vasculitis caused by rabies vaccination, there is localized hair loss at the site of the vaccine which can occur 1-3 months after the vaccine. Some animals with vaccine reaction can later go on to develop more generalized lesions of vasculitis. Some animals with vasculitis can show other symptoms such as lethargy, decreased appetite, fever, muscle disease, joint inflammation, and swelling of extremities.
Diagnosis: Diagnosis of vasculitis is made by clinical signs, diagnostics to identify underlying causes of the blood vessel inflammation (such as bloodwork and testing for infectious or autoimmune diseases), and skin biopsies. Skin biopsies may show inflammation of blood vessels with resultant damage to skin glands and hair follicles. Biopsies taken later in the course of disease may show more non-specific changes such as thinning or ulceration of the skin and loss of skin glands and hair follicles.

Treatment: Treatment of vasculitis involves identifying and treating underlying causes, if possible, and using medications to suppress blood vessel inflammation. Medications which may be effective include steroids, pentoxifylline, the combination of tetracycline and niacinamide, dapsone, sulfasalazine, cyclosporin, or azathioprine. In some cases medication may eventually be discontinued, however some animals will require lifelong medication for control.

Pemphigus foliaceus

Pemphigus foliaceus is an autoimmune disease whereby antibodies produced by an animal’s own immune system attack the bridges that hold skin cells together. It is the most common autoimmune disease diagnosed in dogs and cats.

Dogs and cats of any age or gender can be affected. In dogs, Akitas, Chow Chows, Doberman Pinschers, Dachshunds, and Newfoundlands may be predisposed. No breed predilections exist with cats. Three forms of Pemphigus foliaceus exist in the dog. The first and most common is the spontaneous form which develops in dogs with no history of skin disease or drug history. The second form of Pemphigus foliaceus is initiated via a drug reaction. The third form occurs in dogs with a history of chronic skin disease (e.g. allergies).

Clinical signs: The primary lesion of Pemphigus foliaceus is a pustule. These lesions typically begin along the nasal bridge, around the eyes, and ear pinnae. It is typical for the lesions to spread and occur along the trunk, feet, clawbeds, groin, and footpads. In cats, the nail beds and nipples can also be commonly affected. In most cases, the pustules form and rupture very quickly, so that all that there is left to observe are areas of hair loss, yellow-brown dried crusts, redness and scale. Severely affected animals may become anorexic, depressed and have a fever. The disease itself often displays a waxing/waning course.

Diagnosis: The diagnosis of Pemphigus foliaceus is made by clinical signs, cytology, and biopsy. Other diseases that can appear similar to Pemphigus foliaceus include infection (bacterial, parasitic, fungal), seborrheic skin disease, and varying forms of lupus. Skin scrapes would be performed to rule out external parasites via microscopic analysis. A fungal culture would be done to rule out ringworm (a type of common fungus). Samples of debris from intact pustules or crusts can allow for a diagnosis of Pemphigus foliaceus. In some cases, multiple skin biopsies are required to confirm the diagnosis of Pemphigus foliaceus.

Treatment: Localized cases of Pemphigus foliaceus can be treated with varying strengths of topical steroids. The mainstay of therapy for more generalized cases in both dogs and cats are oral glucocorticoids (e.g. Prednisone). In order to minimize the potential side effects of glucocorticoids (e.g. weight gain, excessive drinking and urinating, liver enlargement), nonsteroidal immunosuppressive drugs are added to the regimen. In dogs, azathioprine and/or cyclosporine can be utilized, while in cats leukeran and/or cyclosporine are the most popular supportive drugs. Other nonsteroidal immunosuppressive drugs include gold salts (dogs and cats) and tetracycline/niacinamide (dogs). Affected animals are started at higher dosages initially until remission is achieved (4-12 weeks), and then are tapered to the lowest possible dosages that maintain remission.