PEARLS, PITFALLS, and DILEMMAS IN DERMATOLOGY

Douglas J. DeBoer, DVM, Diplomate ACVD
School of Veterinary Medicine
University of Wisconsin-Madison

1. MULTIMODAL TREATMENT OF CANINE ATOPIC DERMATITIS

Historically, management of AD has been aimed at the end process of the disease, in other words, focused on anti-inflammatory therapies. "Managing inflammation" has been the first goal of therapy. This traditional approach was a rather "blunt instrument" often consisting principally of oral corticosteroids, with antihistamines or fatty acids as possible adjuncts. As our understanding grew, we gained additional tools to manage the inflammation, for example the oral and topical calcineurin inhibitors such as ciclosporin; and effective topical steroid products that could manage inflammation with less systemic effect. We also gained a renewed understanding of the importance of treating secondary complications such as bacterial and yeast infections. All of these approaches, even as they evolved, were still completely *reactive* – reacting to the inflammatory process, after it had already become well-established in the skin.

Our newer approach to long-term treatment of AD encompasses a broader, "whole-patient" approach, stressing a multifaceted approach, based on a multifaceted pathogenesis, and multifaceted clinical signs that are likely different in each patient. In addition, where possible we now stress a *proactive* approach to treatment – in other words, correcting the underlying pathogenesis of the disease where possible, preventing acute flares where we can, and forestalling the development of chronic inflammatory changes in the skin that become much more difficult to reverse.

The easy way to think about multimodal treatment of AD is to first think of finding the best foundation treatment for each patient. Typically, each dog has "his own best treatment" that, overall, produces the best result. That treatment is typically a drug or biological, though many consider that allergen-specific immunotherapy (ASIT) to be the best foundation treatment for some pets. Selecting the foundation treatment is based on things such as:

- Patient specifics (age, contraindications, etc.)
- Efficacy ("what works" among the major treatments is still largely a matter of trial and error in each patient)
- Cost and value
- Owner compliance and preferences

Along with the foundation treatment, we add on "accessory treatments" to every patient, according to the dog's particular needs. These treatments help the foundation treatment to work, and help to prevent flares or "break-throughs." Things to consider include:

- Elimination of allergens where possible (decreasing allergen load)…targeting environmental, parasitic, dietary, and microbial allergens. Here, *routine parasite control and evaluation for dietary contribution* are most important.
- Control of secondary infections when and as they occur, and *preventing* infections where possible, as opposed to recurring cycles of treatment. *This is one of the most important factors in overall treatment*, yet is often not managed satisfactorily.

- Augmenting or repairing the epidermal barrier in an attempt to limit percutaneous penetration of allergens and irritants. Oral fatty acids may be especially considered here, as they have the most evidence that they help in a variety of situations – most importantly, they are *medication-sparing* (allow less of the primary foundation treatment to be used).
- Modification of the immunologic response through allergen immunotherapy, including new possibilities for an oral "allergy drop" approach

Oclacitinib (Apoquel)

Oclacitinib, a JAK1 inhibitor, has been studied in a variety of models of pruritus and has shown the ability to suppress pruritic responses rapidly and effectively, in some cases better and quicker than prednisolone. At therapeutic doses, oclacitinib inhibits predominantly JAK1 and spares JAK2-dependent processes such as hematopoiesis. Controlled clinical trials of oclacitinib in the treatment of both canine allergic dermatitis (flea, food, contact) and canine AD showed promising results. Results in head-to-head studies against either prednisolone or ciclosporin shows the drug to be equally effective in control of itch and inflammation, and to have a very rapid onset of action with relief sometimes apparent within hours of oral administration. Apoquel is indicated for control of acute or chronic pruritus in dogs over 12 months of age. Recommended dosing consists of twice daily administration for **UP TO** 14 days (important language, as this means twice daily for anywhere between 0 and 14 days), followed by once daily dosing for longer term use. A few dogs seem to worsen slightly when switched from twice to once daily, probably related to the short half-life of the drug (4 hr in the dog). Overall, it appears that at least 60-70% of allergic dogs receiving the drug have rapid, substantial, and prolonged relief of their clinical signs. Veterinary dermatologists involved in early clinical trials often comment that the drug is most useful as PART of a multimodal treatment approach, and that some dogs with even very recalcitrant disease have shown remarkable response. Short-term adverse effects have been limited to GI disturbance in a very few dogs, though the adverse effects occur nearly as frequently in placebo-treated dogs. There is no specific organ toxicity associated with Apoquel, therefore no specific laboratory monitoring is advocated, though good medical practice dictates that all dogs receiving this drug should be examined at least once annually. Apoquel has been administered for as long as 7 years in some dogs; in longer-term studies, occasional patients have developed benign or malignant neoplasms, but no more often than would be expected for dogs in the studied age range. The drug has been limited to use in dogs 12 months or older, mostly because in one high-dose safety study with 6 month old laboratory dogs, generalized demodicosis developed in some patients that were given 5X the label dose. Oclacitinib has not been evaluated in combination with other drugs such as systemic corticosteroids, but recent experience suggests clever ways to use these treatment in stepwise fashion. Apoquel can be used safely along with antibiotics, antihistamines, antifungal drugs, NSAIDs, allergen-specific immunotherapy, and many other medications, and vaccination of treated dogs is effective. Apoquel does not appear to interfere with serologic or intradermal allergy tests. As with other treatments targeting the immune system, it should not be used in the face of a severe infection, demodicosis or with active malignancy.

Recent practical experience with Apoquel by US dermatologists have provided insights as to how best to use the drug. First, two rare adverse effects have been seen, even at the label dose: demodicosis, and slightly lowered WBC count. Until we know more, most dermatologists advise the following examinations if Apoquel will be used longer term: (1) Recheck exams at 2 months, 6 months, and then annually; (2) at each recheck exam, check for lesions or alopecia and if any are present, scrape for *Demodex* mites; (3) serum chemistries and urinalysis are not necessary, though are often recommended as part of general annual health evaluation. Apoquel may not work very well on the pruritus associated with skin infection, either staphylococcal or yeast. Therefore, it is important to treat these infections before using Apoquel (or at the same time) because you will not be able to adequately judge response if

infection is present. Also, think of Apoquel as an antipruritic drug, useful against allergic itch – and not a drug for "any dog with skin disease." It has no effect on noninflammatory alopecia. It is not a substitute for steroids in autoimmune diseases such as pemphigus or autoimmune hemolytic anemia. Some clinicians have observed that it is not always useful in conditions where there is inflammatory swelling, such as severe otitis externa.

Lokivetmab (Cytopoint)

Therapies continue to become more and more targeted. The newest type of therapy in veterinary medicine is monoclonal antibody (mAb) treatment. This therapy has been used in people for about 20 years, and was always considered something that would never be financially practical for dogs or cats. However, improvements in techniques and processes now make it completely possible for this new and dramatically different type of treatment to be accessible for pets. Monoclonal antibody treatments involve treatments with injections of laboratory-produced antibody proteins that target harmful molecules in the pet's body. Because these are proteins that exist normally in the pet, they are not rejected by the immune system, and are not toxic to any organ. They persist for many weeks or even months in the pet's body after subcutaneous injection. These treatments are being developed for a variety of pet diseases such as cancer, pain, and inflammatory disease. Recently, the first anti-itch mAb was approved in many countries for treatment of canine atopic dermatitis. The treatment, named Cytopoint, targets and eliminates IL-31 from the dog's body. After a single injection, the treatment can work in only a few days and can last as long as 8 weeks.

What about safety? First, because these products are peptides or proteins, they are not metabolized by the liver or kidneys, as with a drug, and are not expected to have specific organ toxicity. They are merely degraded into their constituent amino acids, which are recycled for other uses in the body. There is also the possibility that these molecules could become immunogenic. If antibodies are generated which react against the therapeutic substance, at the very least it will be inactivated. At worst, continued administration could result in allergic reactions. In the specific case of lokivetmab (Cytopoint), data from the manufacturer indicates about 3% of dogs will develop "anti-drug antibody" which will render subsequent injections ineffective, though allergic reactions have not been seen. Specific comments:

- Cytopoint appears to work in about 70% of dogs with AD. The dog's response to Apoquel has no relationship to whether Cytopoint will help.
- Cytopoint appears to work mainly against allergic itch. Itch caused by other disease processes, such as skin infections, may not respond.
- Cytopoint may not work against the inflammation itself; for example, the swelling that accompanies allergic ear disease
- Administered at 1 mg/kg (the European label dose), the injection will usually last about 4 weeks. Administered at 2 mg/kg (US Label dose) it can last as long as 6-8 weeks. Both doses have the same initial efficacy; it's just that the US dose lasts longer.
- Cytopoint appears to be remarkably safe, and can be used even in very young dogs.
- Cytopoint can be used along with other drug treatments, if necessary.

Ciclosporin A Modified (CsAM)

The calcineurin inhibitors work by inhibiting production and action of cytokines, and through other mechanisms as well. Clinical trials of ciclosporin in dogs with AD demonstrate that this drug has efficacy equal to that of oral prednisone. The starting dose is 5 mg/kg/day, which can be given as a single dose or divided into multiple doses. After the first month of treatment, in some dogs the dose can be decreased. Perhaps 25% of patients will have some initial gastrointestinal discomfort from CsAM. In most cases, this

will abate within a few weeks. Therapy with CsAM is remarkably free from long-term adverse effects. Gingival hyperplasia is a known adverse effect of longer-term, higher-dose CsAM therapy, but occurs only rarely (1-2% of patients) at the doses typically necessary for AD. Protocols for combination of CsAM with ketoconazole for long-term management of AD have not been developed. A major concern here would be potential for development of hepatotoxicity with long-term ketoconazole treatment. Long-term use of CsAM combined with systemic corticosteroid drugs has been associated with development of fatal opportunistic fungal infections, so should be avoided. CsAM typically acts relatively slowly, often taking 2-4 weeks to reach maximum effectiveness. Therefore, many dermatologists begin a short (2-week) tapering course of oral prednisolone along with CsAM for faster patient relief; this appears safe to do. Therapeutic monitoring (serum chemistries, blood counts, or CsA serum concentrations) is neither recommended nor necessary when using CsAM for AD patients.

APOQUEL	**CYTOPOINT**
Small-molecule, targeted drug that inhibits JAK1 signaling at receptors on neurons and immune cells, thus blocking the action of IL-31 and (to a lesser extent) some other cytokines.	A protein (monoclonal antibody) that binds to and eliminates IL-31 from serum/tissues. Very targeted; cannot affect any other cell processes.
Indication: short-term for allergic dermatitis of any kind (flea, food, environmental); long-term for AD.	Indicated only for canine atopic dermatitis
Oral, once daily for maintenance	SQ injection, once every 4-6+ weeks
Dogs only, >1 year of age	Dogs of any age. Cytopoint is a canine protein; NEVER use in cats – it will cause an immunologic reaction.
Works in ~70% of dogs. Note that Apoquel failure does not correlate with Cytopoint failure.	Works in ~70% of dogs. Note that Cytopoint failure does not correlate with Apoquel failure.
Works on allergic itch. Itch caused by other conditions such as infection may not respond.	Works on allergic itch. Itch caused by other conditions such as infection may not respond.
Anecdotally, may be less effective against the otitis component of allergy in some dogs.	Anecdotally, may be less effective against the otitis component of allergy in some dogs.
Not an all-in-one miracle drug. Must be used along with other elements of multimodal therapy such as infection and parasite control.	Not an all-in-one miracle treatment. Must be used along with other elements of multimodal therapy such as infection and parasite control.
OK when used along with most other medications or ASIT. Not studied (CAUTION) with other immunomodulatory drugs, corticosteroids, etc.	OK when used along with any other medications or ASIT.
Label cautions with severe infections and with pre-existing neoplasia.	No label cautions for comorbidities.
Conventional drug metabolism through liver, then excretion. Not known to have any specific organ toxicity.	Eventually broken down into amino acids, which are recycled and used again for other protein synthesis. Not really possible to have any organ toxicity.
Short-term adverse effects may include rare instances of vomiting; longer-term, demodicosis and mild anemia have been reported anecdotally.	No short-term adverse effects seen. Longer-term, no adverse effects, but rare dogs develop anti-drug antibody which renders further treatments ineffective.
Monitoring not critical, but good to monitor blood counts 1-2x yearly.	No monitoring necessary or recommended.

2. GET READY FOR RESISTANCE: STAPHYLOCOCCAL SKIN INFECTIONS

- Staphylococcal skin infections are increasingly difficult to treat in dogs, because of antimicrobial resistance. Unfortunately, many years of treating pyoderma with repeated courses of antibiotics has led to the recent and increasing appearance of multi-drug-resistant staphylococci.
- In some areas of the world, more than 50% of skin cultures performed at dermatology specialty practices are methicillin-resistant staphylococci (MRS). These strains include the methicillin-resistant *Staphylococcus pseudintermedius* species (canine infections, referred to as "MRSP") or methicillin-resistant *Staphylococcus aureus* species (human infections, referred to as "MRSA" and, fortunately, much less common).
    - Veterinarians should endeavor to use correct terminology when discussing these infections with clients; incorrectly referring to a canine MRSP infection as "MRSA" may be alarming to the client.
- If laboratory testing indicates the presence of MRS, the isolate will be *clinically resistant to all penicillins and cephalosporins*. In addition, some MRS will also be resistant to other antibiotic classes, such as fluoroquinolones or clindamycin.

What's the Practical Significance?

- If you treat a dog with staphylococcal pyoderma with a beta-lactam antibiotic (cephalosporin or amoxi/clav) and there is limited or no response, *culture and susceptibility testing is now mandatory*. If you do identify an MRS organism, you should obtain a staph speciation test to determine if the organism is a human or veterinary strain.
- Fortunately, many veterinary strains of MRS are still susceptible to routine antibiotics such as trimethoprim-sulfamethoxazole, clindamycin, or a fluoroquinolone such as enrofloxacin or marbofloxacin. However, it is important to note that it is impossible to predict with any certainty which antibiotics are indicated without performing a susceptibility test. Empirical "antibiotic hopping" is hazardous, as with each cycle of treatment, multiple drug resistance becomes more likely.
- If you have a patient with MRSP (i.e., the canine strain) in your hospital, you need not have the dog under full isolation conditions, but you should isolate the patient to the extent you can and eliminate traffic from this patient to other dogs in the clinic, especially waiting room, surgery, and critical care areas. Especially important to practice good hygiene measures.
- If the organism is a methicillin-resistant, human-origin *S. aureus* (MRSA), the owner should be notified of this fact so they can discuss the situation with their own health care provider, and gloves should be worn when examining the patient. If hospitalized, consider full isolation. This patient is a <u>potential</u> human health hazard and should be considered so until all lesions have completely resolved. The concern here is that without proper precautions, the MRSA could colonize the owner, you, your staff, or others.
    - It is important to understand that merely becoming colonized with MRSA is not inherently dangerous.
    - MRSP or MRSA strains are not really more 'virulent' than other staph strains; they are just more difficult to treat.
- *KEY TAKEAWAYS: if pyoderma is poorly responsive, culture. You want to know not only the susceptibility, but also the species, as this determines both treatment and potential hazards.*

Exploring Solutions: Patient Treatment

- The emergence of MRS in the veterinary world suggests that we must redouble our efforts to use antibiotics wisely and judiciously and reconsider all efforts to use alternative, nonantibiotic treatments, if possible, especially in the face of recurrent infections.
- Increasingly, dermatologists understand that it is very possible to *eliminate* active superficial staphylococcal infections (even MRS) from the skin by using topical products as the primary treatment without antibiotics. For primary treatment of an existing superficial pyoderma, *daily* treatment is necessary until the infection is cleared, which typically takes 3 weeks or more.
- Antimicrobial topicals are also the first line of defense for *prevention of relapse* in patients with recurrent pyoderma where the cause cannot be found or treated. For preventive maintenance, topicals are typically used 2-3 times weekly.
- Spray-on, wipe-on, leave-on, or mousse products are often preferable to shampoos for frequent or long-term use, as they both provide residual effect and improve client compliance. Whether used daily as primary treatment or every few days as preventive maintenance, the following ingredients are useful in topical products:
    - Chlorhexidine— 2-4% spray, mousse, or gel, for treatment or prevention. This is the most-studied ingredient. Miconazole is synergistic with chlorhexidine, so a combination product is probably best.
    - Daily wipe-down (of the pet) with alcohol-gel hand sanitizer. Though unstudied, this treatment is reportedly very effective and is used commonly in the Nordic countries.
    - Use of oxidizing disinfectants such as very dilute sodium hypochlorite solutions ("bleach baths") has become very popular in human atopic dermatitis recently to limit bacterial colonization of skin. Veterinary products with similar actions are gaining popularity with some dermatologists, although critical studies are lacking.
- *KEY TAKEAWAY: When you see superficial pyoderma, think topical first!*

Exploring Solutions: Sanitation and Public Health

- MRS is spreading very fast in both the human and veterinary world. It is time to start taking every precaution to prevent transmission of MRSP strains in your clinic, and prevent colonization of humans by MRSA.
- Key measures for sanitation have been developed by expert panels, and include:
    - Handwashing and disinfection; wearing gloves when appropriate
    - Protective clothing, with frequent laundering
    - Cleaning and disinfection of premises. Use one examination room for skin cases only!
    - Education of staff and pet owners
- *KEY TAKEAWAYS: Explore these very valuable online resources!*
    - Most recent international expert panel recommendations for diagnosis and treatment of pyoderma, published April 2014. Great reference. http://onlinelibrary.wiley.com/doi/10.1111/vde.12118/abstract (click on "get PDF" on the right to see the whole article)
    - A superbly interesting and entertaining blog site about zoonoses; provides great information. Recommended lunchtime reading! Click on "Resources-Pets" to access downloadable client handouts on MRS, etc. www.wormsandgermsblog.com

3. FELINE FACIAL DERMATOSES

Feline facial dermatoses represent a reasonably common clinical complaint, but a very wide variety of underlying diseases.

Parasites
Facial dermatitis related to a parasite is most commonly related to a mite infestation, rather than to something more common like fleas or cheyletiellosis. Feline scabies (*Notoedres*) is rare, but causes an extremely pruritic dermatitis of the face and neck. One of the newly-described *Demodex* mites, such as 'gatoi' or the 'unnamed' mite may cause contagious, pruritic facial dermatitis. The good news is that all of these mites are easily found, and easily treated!

Infection
Not a common primary cause of dermatitis restricted to the face, with the strong exception of dermatophytosis. Nevertheless, cytology should be routinely performed to check for any bacterial of yeast overgrowth, which is typically secondary. Wood's lamp examination and culture are mandatory in ANY facial dermatitis, no matter the appearance. The other important infectious cause of facial dermatitis is feline herpesvirus 1 (FHV1). Though rare, this aberrant infection causes severe ulcerative, necrotic, erosion to plaquelike lesions on the face which may be mistaken for other diseases such as eosinophilic granuloma. This is a good example of why it is important for any cat with persistent, rather severe, ulcerative facial dermatitis to be biopsied; generally the virus can be found by direct histologic examination or PCR. Treatment is generally very effective, using the *newly established recommended dose* of famciclovir at 90 mg/kg orally twice daily for 3+ weeks

Allergic Disease
In theory, food allergy, environmental allergy, or insect allergy can all manifest as facial dermatitis. Of these, food allergy should be a primary suspect in feline head/neck pruritus and dietary restriction/provocation trials are mandatory.

Pemphigus Foliaceus
The most common autoimmune skin disease of cats, PF typically has a strong component of facial distribution, particularly on the bridge of the nose, around the eyes, and on the ear pinnae [2]. Most cats also have involvement of their footpads and/or nailbeds ('caseous paronychia') but this is not always the case. The clinical appearance of PF is rather dramatic and unusual, however, it is important that biopsy confirmation is always obtained for this disease: there have been reports of PF-like disease in cats caused by primary infections, particularly with dermatophytes.

Feline Acne
There is much 'myth and legend' over the causation of feline acne. Most cases are probably idiopathic, perhaps with a cause similar to that in humans – defective cornification in the follicle or sebaceous duct leading to "plugging" with keratinaceous debris and secondary infection. Rarely, a defined cause such as primary bacterial infection or dermatophytosis may be responsible. Causes such as the type of food bowl, food allergy, failure of chin grooming, etc. are much more speculative and there is no convincing evidence for this pathogenesis. Treatment relies initially on clearing any secondary bacterial infection with antibiotics, then providing daily facial hygiene with keratolytic topical products (2-3% benzoyl peroxide, or salicylic acid), which may need to be done periodically on a longterm maintenance basis. For recalcitrant cases, the author has had success with topical tretinoin gel or cream (0.025%, applied twice daily until resolution and then once every 1-2 days to maintain remission if needed).

"Dirty Face" in Persian cats is an uncommon but frustrating idiopathic facial dermatitis that is considered by some to be a more severe form of feline acne. In this disease, comedones and crusts extend beyond the chin area to the facial folds and preauricular areas. Diagnostic evaluations should be performed as above to rule out definable causes, but most cases are idiopathic and may be a genetic alteration in this breed. Therapy is symptomatic, using topicals as for feline acne.

Indolent Ulcer
Indolent ulcers appear as well-demarcated ulcer with raised borders present on the margin of the upper or lower lip. Initial diagnosis is generally straightforward, based on clinical appearance and cytology: remove surface debris with a gauze pad to expose the most underlying tissue and take impression smears. The finding of eosinophils on cytology is sufficient to make an initial tentative diagnosis. Note if cocci are also found, especially intracellularly, and if they are found, treat first with antibiotics as this disease can sometimes reflect an aberrant response to bacterial infection. In an otherwise healthy, young animal, it is acceptable to treat the cat with ONE course of injectable corticosteroids (20 mg methylprednisolone acetate, every 2 weeks for a total of 3 injections). If the disease is especially severe, recalcitrant, or recurrent, a search for an underlying cause, should be made (including biopsy with assessment for FHV1 presence) and repeated corticosteroid use should be avoided. Recalcitrant cases of idiopathic origin can often be successfully treated with ciclosporin, but a higher dose is often necessary – start at 10-15 mg/kg/d for the first 2-4 weeks; if effective, then gradually taper.

4. TOP TIPS FOR RECURRENT OTITIS

Otitis externa is very common in daily practice, accounting for 15% or more of canine patient visits. Yet, this important disease is often frustrating to treat, particularly when the condition is recurrent or chronic. This lecture will focus on everyday otitis, or otitis that is episodic but recurrent – that is, ear disease that clears when treated, but then recurs. This condition has profound implications for both the owner and the veterinarian. It is expensive and emotionally difficult for owners, and can lead to loss of confidence and dissatisfaction with care.

Tip 1. Better Diagnosis with Cytology and Culture
There is no reliable correlation between the gross appearance of otic exudate and the causative organism. Ear cytology is really the only method that can help to uncover the bug! Knowing the organism is an important determination in initial treatment. Cytology is a quick way to monitor progress at rechecks, and generates medically-justified revenue. *The main question in ear cytology is: are the organisms cocci, rods, yeast, or a mixture?*

Ear cytology is easy and quick, and an ideal procedure to teach your technicians. Insert a swab carefully and gently into the vertical ear canal, roll (do not smear) the contents onto a microscope slide, and heat-fix gently (especially if the exudate appears greasy). Any routine "Dif-Quik" hematology stain can be used. Examine using a good, well-maintained microscope and use 1000X oil-immersion. There are several possible cytologic results:

- Cocci. Here, there's little problem, because this most likely represents growth of normal ear flora, and is unlikely to be antibiotic-resistant – though this is possible. But – check for inflammatory cells!!
- Yeast. Again, little problem, and easy to treat.
- Ceruminous debris, with few or no organisms. Inflamed, itchy ears without growth of microorganisms most likely indicates an allergic underlying etiology.

- Inflammatory cells. Here, caution is warranted, as the infection has gone beyond just "surface overgrowth" and is heading towards a soft-tissue infection.
- Rods. Caution here – more difficult to predict susceptibility and empirically choose an antibiotic. Important to recheck, and warn owner.

When should you consider a culture and susceptibility? Not for first-time, routine otitis. However, if the otitis is resistant to initial treatment or recurrent, especially if rods are present, it is clearly indicated. Remember, too, that this test reports susceptibility of organisms to tissue or plasma concentrations of antibiotics, and therefore is mostly relevant to choose a systemic antibiotic for more severe cases. The concentration of antibiotics in otic preparations is typically hundreds of times that attainable in plasma, so an "intermediate" result for an antibiotic means that the drug will probably work if used topically.

Tip 2. Know Your Products: What Do I Reach For?
Which antibiotic? More than 80% of "everyday" otitis involves *Malassezia, Staphylococcus*, or both. Staph organisms USUALLY have broad susceptibility and any of the common aminoglycoside antibiotics should be effective. Fluoroquinolone antibiotics are best reserved for *Pseudomonas* or other gram-negative bacteria WITH the appropriate susceptibility result. Polymyxin B is another possibility – it has increased activity against gram-negative rods and could be considered as an alternative here. Bear in mind that this antibiotic is made less effective by exudate in the ear canal, so the ear must be clean to use it! The newest antibiotic to appear in ear preparations is florfenicol. This antibiotic is similar to chloramphenicol; it is best used for otitis where cocci are present, as its activity against rod bacteria is highly variable and it is ineffective against *Pseudomonas.*

Which antifungal? If the organism involved is yeast, virtually any antifungal will work. "Resistance" of *Malassezia* to antifungals has been reported extremely rarely. One misconception is that if yeast otitis is recurrent, it is a failure of antifungal treatment. Rather, this clinical situation reflects a continuing underlying inflammatory ear condition, usually allergy, and calls for corticosteroids rather than a different antifungal!

Which steroid? Almost all topical ear therapeutics contain a corticosteroid, usually a low to moderate potency drug and all are reasonably equivalent. Newer use of the "soft" steroids such as hydrocortisone aceponate or mometasone have the possibility of providing good anti-inflammatory action with less chance of adverse effects. Use of a steroid in the ear is critically important. It reduces physical narrowing of the canal, reduces cerumen secretion, and therefore makes it much more difficult for organisms to grow.

What if the tympanum is ruptured? Well – first of all, most of the time it's difficult to tell if the TM is ruptured. Ototoxicity varies by species, and in dogs the data is incomplete and conflicting. We can say unequivocally that chlorhexidine is ototoxic if used at >0.2%, and I avoid it completely in cats. Common sense ways if the TM is obviously damaged, avoid the aminoglycosides if possible, but don't worry too much about it.

Tip 3. To Clean or Not to Clean – and When?
The simple answer here is: CLEAN! But, it's a little more complex than that, and opinions vary widely. There is no question that debris, cerumen, and pus in the ear canal creates food, moisture, and "hiding places" for growth of microorganisms, impedes flow and efficacy of topical preparations, and inactivates some antimicrobials. Thus, initial cleaning of an infected ear (in the clinic) is important. Depending on how severe and sore the ear is, this may be done with or without sedation. This author's bias is that the

more gentle you can be, the better. Using mild, pH neutral detergent or solvent solutions is best in an inflamed, sore ear. Demonstrate to the owner how to hold the pinna up, instill the cleaner into the ear canal without touching the tip to the pinna, massage the canal to loosen and solubilize the debris, and then wipe or blot it out with a gauze pad around a finger. Repeat until the material being blotted is no longer colored or laden with debris. BE GENTLE!

There are two reasons that "cleaning solutions" are used: (1) to physically soften, dissolve, and remove debris; and (2) to leave an antimicrobial ingredient in the ear, to help with limiting growth of organisms. Reason (1) is most important in initial treatment. Choose a cleaner that is effective at loosening debris, yet gentle. I avoid use of acid-containing or low-pH cleaners in a sore ear. Once the ear has healed, and the goal is more the antimicrobial action, you can think more about the antiseptic ingredient. The latter is especially important in long-term "preventive maintenance." Once the ear is initially cleaned in the clinic, have the owner apply topical medication per label instructions. My bias is to recommend no cleaning for the first 3-4 days, until the ear is more comfortable. At that time, the owner may begin GENTLE cleaning (as you have demonstrated) every 2-3 days if and as debris accumulates.

Tip 4. The 5 Causes of Recurrent Otitis

When otitis is recurrent, there are really only 5 reasons why this situation exists. Note that there might be just one reason, or any combination of:

- An antimicrobial-resistant organism
- Ear pathology causing persistent stenosis or occlusion; this includes stenosis from edema, hyperplasia, or scarring; and occlusion from the same or from a mass lesion.
- A persisting underlying cause that has not been addressed (the most common are allergy and primary seborrhea)
- Otitis media is present and has not been treated
- The owner is unable to comply with your recommended treatment

The key to successful treatment of recurrent otitis is to carefully consider each of these causes, one by one, determine which are present, and take steps to resolve each one.

Tip 5. Maintenance Therapy

Maintenance therapy of ear disease is one of the most valuable, though most overlooked, aspects of dealing with recurrent conditions. Typically, maintenance therapy will consist of:

- Regular cleaning at home (every 1-2 weeks), with an ear cleaner that contains an antimicrobial ingredient. This both removes debris, and makes the ear inhospitable to further growth of organisms. The author has seen most success with products containing either chlorhexidine or microparticulate silver.
- Often, regular application of a corticosteroid-only ear drop. Start daily, and then taper every 2-7 days as proactive *preventative* therapy. It is best NOT to use an antibiotic-steroid combination product long-term, as intermittent use of an antibiotic is a great way to lead to bacterial resistance!! Products containing 1% hydrocortisone are often too weak in potency to help much. Fluocinolone/DMSO drops (Synotic®, Zoetis) is the only moderate-potency, steroid-only ear drop that is made commercially. As an alternative, the author routinely uses a solution of 1 mg/ml dexamethasone in propylene glycol. To formulate this, mix one part of propylene glycol with 1 part of dexamethasone injection (the 2 mg/ml product). This is an inexpensive and effective longer-term treatment for inflammatory ear disease.