

## DISPELLING THE OTITIS MYTHS IN VETERINARY MEDICINE

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Many myths regarding the diagnosis and treatment of otitis externa have anchored their way into the general veterinary practice. These misconceptions have contributed to our lack of discretion when selecting antimicrobials and improper interpretation of laboratory findings leading us to reach for medications that should normally be used in severe and truly resistant cases of otitis externa. My aim with this seminar, is to dispel those myths and improve our diagnostic and therapeutic approaches to otitis externa.

From historical, to diagnostic to therapeutic and finally client education myths, let's start our journey into facts and not myths:

### 1. Otitis externa is a primary diagnosis

Otitis is rarely a primary diagnosis on its own. There are multitudes of underlying etiologies that cause otitis externa along with predisposing and perpetuating factors. Therefore treatment of repeated bouts otitis externa should always encompass a search and treatment of the underlying etiology to prevent further flares. When dealing with allergies, will often take a "cut through the onion" approach rather than "peeling the onion"; that is, I address food allergies with a dietary trial, and at the same time I treat environmental allergies symptomatically and use adulticides systemically and topically to control flea allergies. By taking this multi-pronged approach to bring allergens below your patient's allergic threshold, you will hasten my patient's response, often controlling their underlying cause of allergic otitis within 4 weeks.

**Morris** DO. Medical therapy of otitis externa and otitis media. *Vet Clin Small Anim* 2004;34:541-555

**Noxon** JO, Roudebush P. 10 things Every Practitioner Should know about canine ears. *About Canine Ears - Hillsvet.com* (open access)

### 2. Swimmer's Ear exists in our pets

Moisture in the ear is only an issue if inflammation is present (likely due to allergies). The hot ear canal with water added will act as an incubation chamber for the bacteria. Note that for every Labrador retriever that develops an ear infection after swimming, there are another 499 Labradors that simply shake their head and go about their business.

### 3. Cockers and Labs need cleansing regularly

Cerumen (wax) has bacteriostatic and fungistatic properties that help to control the microbiome within the ear canal (Huang et al). Earwax is produced in excess in hypothyroid individuals and as a protective mechanism during an inflammatory event. However, for every Cocker Spaniel and Labrador retriever with ceruminous otitis externa, there are another 499 that are normal without any evidence of ear disease. Dealing with the underlying etiology and inflammation will normalize the cerumen production and eliminate the need to regularly cleanse the ears.

**Huang** HP, Fixter LM, Little CJ. Lipid content of cerumen from normal dogs and otitic canine ears. *Vet Rec.* 1994;134:380-381

**Noxon** JO, Roudebush P. 10 things Every Practitioner Should know about canine ears. *About Canine Ears - Hillsvet.com* (open access)

### 4. Ear medications can only be used for 7-14 days

ACUTE otitis would represent a one-time, short duration (~7-14 day) ear infection. CHRONIC otitis is characterized by ear infections lasting greater than 14 days and/or recurrent in nature. In ACUTE cases, manufacturers' recommendations should be followed. With CHRONIC cases, repeated courses of ACUTE therapy may be required along with addressing the underlying etiology and potential systemic anti-inflammatory therapy such as glucocorticoids or cyclosporine. Dosing and duration of the systemic anti-inflammatory medication is based on the severity of the ear infection.

### 5. Diagnosis by smell and discharge

Diagnosing the infectious agent by smell and discharge is often misleading. Brown discharge can be attributable to *Malassezia*, cocci and *Otodectes*. Purulent discharge with ulceration is often associated with *Pseudomonas* but may also be caused by *Candida albicans* and adverse drug reactions. Likewise, the predictability of odour to provide insight regarding the infectious organism is not only poor, but also potentially dangerous, especially considering the incidence of Methicillin-Resistant Staphylococcal organisms.

### 6. Selection of topically applied ear medications should be based on bacterial culture/sensitivity findings

Otic cytology is quantitative, giving the clinician a rapid indication of the relative number of morphologically different species present in the ear, which may aid in empirical selection of otic therapy. Discordance between cytology and otic cultures has been reported by Graham-Mize et al and Schick et al, and for this reason, it must be emphasized that otic cultures should always be interpreted with reference to concurrent cytology done by the

clinician at the time of sampling, and the results of both these diagnostic tests should be interpreted in light of the otic examination. As well, otic cultures are fraught with many challenges and controversies:

- 1) They do not reflect concentrations within the topical ear products, which typically achieve 10-1000 times the concentration of what can be delivered (Hillier; Robson et al)
- 2) They do not account for biofilm producing microorganisms that may increase the concentration of antimicrobials necessary to kill the protected organisms (Pye et al)
- 3) They do not account for the synergism between medications that are contained within the topical ear medications (e.g Surolan and miconazole) (Boyen et al; Chiavassa et al)
- 4) They only reflect *in vitro* sensitivities and do not take into account the *in vivo* factors such as pus, ceruminous debris, microbiome and microenvironment

Hence I tend to only pursue otic bacterial culture and sensitivity when:

- 1) The therapeutic plan involves systemic antibiotic therapy because the owners are unable to use topical therapy
- 2) When otitis media is present (head tilt), as systemic antibiotics are indicated.

**Boyen F, Verstappen KM, De Bock M, Duim B, Weese JS, Schwarz S, Haesebrouck F, Wagenaar JA.** In vitro antimicrobial activity of miconazole and polymyxin B against canine methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus pseudintermedius* isolates. *Vet Dermatol.* 2012 Aug ;23(4):381-5, e70

**Chiavassa E, Peano A, Pasquetti M, Vaara M** Evaluation of In Vitro Synergistic Interaction of Miconazole and Polymyxin B Against Clinical Strains of *Malassezia pachydermatis*. *The Open Mycology Journal*, 2013;7:7-10

**Graham-Mize CA & Rosser EJ.** Comparison of microbial isolates and susceptibility patterns from the external ear canal of dogs with otitis externa. *JAAHA* 2004;40:102-108

**Hillier A.** Treatment of *Pseudomonas* otitis in the dog. 2005 *Veterinary Medicine DVM360* (<http://veterinarymedicine.dvm360.com/vetmed/article/articleDetail.jsp?id=179408>)

**Pietschmann S, Hoffmann K, Voget M, Pison U.** Synergistic effects of miconazole and polymyxin B on microbial pathogens. *Vet Res Commun.* 2009;33(6):489-505

**Pye CC, Yu AA, Weese JS.** Evaluation of biofilm production by *Pseudomonas aeruginosa* from canine ears and the impact of biofilm on antimicrobial susceptibility in vitro *Vet Derm* 2013;24(4) 446-e99

**Robson D et al.** Correlation between topical antibiotic selection, in vitro bacterial antibiotic sensitivity and clinical response in 16 cases of canine otitis externa complicated by *Pseudomonas aeruginosa*. *Vet Derm*, 2010;21:311-328

**Schick A et al.** Variability of laboratory identification and antibiotic susceptibility reporting of *Pseudomonas* isolates from dogs with chronic otitis externa. *Vet Derm* 2007;18(2):120-126

## 7. **Ingredients don't matter...they all have an antibiotic, antiyeast and anti-inflammatory agent...and they all work the same**

Rather, one should choose ear products based on ingredients not the name. When choosing an ear medication, be certain that it contains the necessary ingredients to address what you have identified on cytology. Choose ingredients with the greatest efficacy (Hariharan et al; Peano et al) and highest safety margins that are applicable for the dosing regimen outlined. Also, to help minimizing overstocking of ear medications in your practice, choose effective ear medications with polar opposite ingredients (e.g. Mometamax® and Surolan®) so that if an incomplete response is noted with one product, you will have a different spectrum of antimicrobial action with the other medication.

**Hariharan H, Coles M, Poole D, Lund L, Page R.** Update on antimicrobial susceptibilities of bacterial isolates from canine and feline otitis externa. *CVJ* 2006;47 253-255

**Peano A, Beccati M, Chiavassa E, Pasquetti M.** Evaluation of the antifungal susceptibility of *Malassezia pachydermatis* to clotrimazole, miconazole and thiabendazole using a modified CLSI M27-A3 microdilution method *Vet Derm* 2012;23(2)-131-e29,

## 8. **An antibiotic kills bacteria and an antiyeast kills Malassezia**

In fact, there have been several studies that have looked at the action of clotrimazole, which not only addresses yeast but also gram-positive bacteria including MRSA (Alsterholm et al; Cui et al). Other azole-derivatives such as miconazole have also been shown to have similar antibacterial activity (Weese et al). As well, polymyxin B has excellent activity against gram-negative rods but has also demonstrated antiyeast activity (Chiavassa et al). By combining these two ingredients, it has been demonstrated that polymyxin B increases the efficacy of hydrophobic antimicrobials by facilitating penetration into the bacteria so that miconazole can more readily reach the intracellular space increasing its efficacy (Boyen et al; Chiavassa et al; Pietschmann et al). As well as it's known ability to inhibit the synthesis of ergosterol, a key component of fungal cell wall, azole-based products can also induce reactive oxygen species which results in fungal cell death (Francois et al; Ghannoum et al). Therefore scrutinizing studies that report decreased efficacy based solely on evaluation of individual antibacterial ingredients *in vitro*, such as that reported by Pye et al in combination with Tris-EDTA, an agent that helps to breakdown biofilm and increase penetration into gram negative bacteria, needs to be taken with a grain of salt as they did not take into account the synergism of the sum of ingredients.

**Alsterholm M, Karami N, Faergemann J.** Antimicrobial Activity of Topical Skin Pharmaceuticals – An In vitro Study. *Acta Derm Venereol* 2010; 90: 239-245

**Boyen F, Verstappen KMH, De Bock M, Duim B, Weese JS, Schwarz S, Haesebrouck F, Wagenaar JA.** In vitro antimicrobial activity of miconazole and polymyxin B against canine MRSA and MRSP isolates *Vet Derm* 2012;23(4) 381-e70

**Chiavassa E, Peano A, Pasquetti M, Vaara M.** Evaluation of In Vitro Synergistic Interaction of Miconazole and Polymyxin B Against Clinical Strains of *Malassezia pachydermatis*. *The Open Mycology Journal*, 2013;7:7-10

**Cui S, Han L, Xiao S, Chen X, Chang Q, Liu Y, Zhang X.** Investigation of antibacterial activity of topical antimicrobials against methicillin-resistant *Staphylococcus aureus*. *Chinese Journal of Burns* 2014; 30(1):21-24

**Francois IE, Aerts AM, Cammue BP, Thevissen K.** Currently used antimycotics: spectrum, mode of action and resistance occurrence. *Curr Drug Targets* 2005; 6: 895-907

**Ghannoum MA, Rice LB.** Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. *Clin Microbiol Rev* 1999;12:501-517

**Pietschmann S, Meyer M, Voget M, Cieslicki M.** The joint in vitro action of polymyxin B and miconazole against pathogens associated with canine otitis externa from three European countries *Vet Derm*2013;24(4) 439–e97

**Pye CC, Singh A, Weese JS.** Evaluation of the impact of tromethamine edetate disodium dihydrate on antimicrobial susceptibility of *Pseudomonas aeruginosa* in biofilm in vitro *Vet Derm* 2014;25(2) 120–e34

**Weese JS, Walker M, Lowe T.** In vitro miconazole susceptibility of methicillin-resistant *Staphylococcus pseudintermedius* and *Staphylococcus aureus* *Vet Derm* 2012;23(5) 400–e74

## 9. Ototoxicity is associated with topical ear medications

In an ear with a ruptured tympanic membrane, ototoxicity is not an issue with TOPICAL aminoglycosides or most other antibiotics, as long as the oval and round windows dividing the middle from the inner ear are intact. Co-administration of Vitamin E or aspirin with ear medications may prevent hearing loss in predisposed individuals (more mature pets)

**Noxon JO, Roudebush P.** 10 things Every Practitioner Should know about canine ears. About Canine Ears - Hillsvet.com (open access)

**Oishi N, Talaska AE, Schacht J.** Ototoxicity in dogs and cats. *Vet Clin North Am Small Anim Pract.* 2012;42(6):1259-1271

**Strain GM, Merchant SR, Neer TM, Tedford BL.** Ototoxicity assessment of gentamicin sulfate otic preparation in dogs. *AJVR* 1995; 56(4); 532-538

In a recently presented study by Mason et al based on a comparison of BAER and owners' ability to detect hearing loss in their pet, owners were able to detect whether their pet was perfectly normal or moderately to profoundly BILATERALLY deaf (BILATERAL Grade II; Grade III; Grade IV) with 100% certainty. Owners were not however able to detect slight (Grade I), moderate (Grade II) and severe (Grade III) UNILATERAL hearing loss at all. Therefore hearing loss in dogs may have either pre-existed the start of topical medication or the topical medication may act as a physical barrier for sound waves as most treatments are either a fluid or viscous ointment. Discontinuing use of the topical medication in question along with flushing the ear(s) once daily for 7-14 days using saline should help restore hearing to its original level prior to treatment.

**Mason CL, Susan Paterson S, Cripps PJ.** Use of a hearing loss grading system and an owner-based hearing questionnaire to assess hearing loss in pet dogs with chronic otitis externa or otitis media. *Vet Derm* 2013;24(5):512–e121

## 10. Anti-yeast resistance is rampant in Canada

In multiple studies (Peano et al, Weiler et al), miconazole and clotrimazole have very similar efficacy profiles. The concept that clinical failure is linked to increased MICs is debatable, as most antifungal concentrations in topical ear products are 100-1000 times higher than the MIC. As well, laboratory methods for testing sensitivities of yeast are only now coming to light but have yet to be standardized. Regional variation may certainly contribute to perceived resistance or lack of efficacy, but in general, both are efficacious. As well, newer product lines that contain terbinafine (Osumnia®, Elanco) and posaconazole (Posatex®, Merck) will reach the Canadian market to provide other alternatives in case a yeast resistance is suspected.

**Peano A, Beccati M, Chiavassa E, Pasquetti M.** Evaluation of the antifungal susceptibility of *Malassezia pachydermatis* to clotrimazole, miconazole and thiabendazole using a modified CLSI M27-A3 microdilution method. *Veterinary Dermatology* 2012;23(2):131-135

**Weiler CB, Kunz de Jesus FP, Nardi GH, Loreto ES, Santurio JM, Coutinho SDA, Alves SH.** Susceptibility variation of *Malassezia pachydermatis* to antifungal agents according to isolate source. *Braz J Microbiol* 2013;44(1)

## 11. Drop versus cc equivalent

Each drop from a bottle of ear medication is typically standardized to deliver 0.025ml. Therefore, the total daily volumes of products delivered as drops typically range per label from 0.1 ml (4 drops per day) to 0.5 ml (10 drops twice daily). The volume of the external ear canal has been determined by various methods to range from 0.5-2.5 cm<sup>3</sup> (Bloom, Forsythe). Using fluorescent dye studies to label ear treatment products, it has been reported that it takes 0.5 to 1 ml of medication to get down to the tympanic membrane in dogs (Noxon et al, Flinn et al).

**Bloom P.** Practical approach to diagnosing and managing ear disease in the dog. Michigan Veterinary Conference, 2007

**Flinn A, Noxon JO.** Comparison of two techniques to determine ear canal volume in the dog. Iowa State Univ Summer Scholars Program 2012

**Forsythe WB.** Tympanographic volume measurements of the canine ear. *AJVR* 1985;46(6):1351-1353

**Noxon JO, Roudebush P.** 10 things Every Practitioner Should know about canine ears. About Canine Ears - Hillsvet.com (open access)

With these facts in mind, we recommend administering the following to achieve sufficient contact and concentration of ear medications while treating an infection:

Small dog or cat	e.g. Yorkshire terrier	0.25ml	10 drops
Medium breed dog	e.g. Cocker spaniel	0.5ml	20 drops

Large breed dog	e.g. Golden retriever	0.75ml	30 drops
Giant breed dog	e.g. Newfoundland	1.0ml	40 drops

Be certain to dispense the correct quantity to equal the labeled treatment course as this will avoid contamination of ear products as well as owners having insufficient volumes/ concentrations of medication when trying to make the bottle last for another treatment course. As recontamination of an ear when cleansing can be a cause for recurrence, utilization of individual pipettes or small containers is ideal so that the containers can be discarded after one use or one treatment course.

**Bartlett SJ**, Rosenkrantz WS, Sanchez S. Bacterial contamination of commercial ear cleaners following routine home use. *Veterinary Dermatology* 2011; 22(6):546-553

**Kirby AL**, Rosenkrantz WS, Ghubash RM, Neradilek B, Polissar NL. Evaluation of otoscope cone disinfection techniques and contamination level in small animal private practice. *Veterinary Dermatology* 2010;21(2):175-183

## 12. Compounded ear products better than formulated

The sale and application of compounded products has many potential implications, which should be considered. These include safety factors, quality, potency, and efficacy. The legislative veterinary bodies have a hierarchy of medication selection that veterinarians should legally abide by as follows (CVMA July 2010 - Decision Cascade for legitimate use of drugs in veterinary practice):

- a) Veterinary licensed - on-label use
- b) Veterinary licensed - extra-label use
- c) Human licensed drug – extra-label use
- d) Compounded drug – from approved veterinary drug
- e) Compounded drug – from approved human drug
- f) Compounded drug – from active pharmaceutical ingredient

To summarize the key points: 1) Otitis externa is NOT a primary disease; 2) Allergies and hypothyroidism are top causes for recurrent otitis externa; 3) Cytology is a key diagnostic tool in dermatology; 4) Current cultures are not indicated for selection of topical ear medications; 5) Selection of products for the practice should be based on the active ingredients