REVIEW

Topical ear treatment – options, indications and limitations of current therapy

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Topical otic products form an integral part of the overall management of otitis externa. With an ever increasing array of ear drops and cleaners to choose from, appropriate selection of therapy can be difficult. The investigation of all cases of otitis externa should consider primary and secondary causes and predisposing and perpetuating factors. This article considers topical therapy under these same broad headings and discusses, through literature review, the various properties of the components of the ear cleaning solutions and drops.

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INTRODUCTION

Whilst the management of otitis externa (OE) and otitis media (OM) involves more than just topical therapy, there is no doubt that unless appropriate topical ear cleaners and prescription ear drops are selected, ear disease will not resolve. Griffin has proposed a new classification of OE that divides the aetiology of the disease into primary and secondary causes (Tables 1 and 2) which are respectively diseases or infections that directly cause inflammation in the ear, and perpetuating or predisposing factors (Tables 3 and 4) which are agents or elements that contribute to ear disease (Griffin 2010). Based on this classification, the key steps in successful therapy of otitis are to diagnose and manage primary skin diseases affecting the ear, identify and treat secondary infections and then recognise any perpetuating or predisposing factors and manage them to prevent recurrence of disease. Rather than list and discuss all of the different available topical otic products this review will consider how topical therapy can best be used to manage each of these components of ear disease.

TOPICAL THERAPY TO MANAGE PRIMARY CAUSES OF OTITIS

The most important causes of OE are listed in Table 1. Allergy is the most common of the primary triggers and can account for up to 75% of all cases (Paterson 2002, Saridomichelakis *et al.* 2007, Zur *et al.* 2011). If otitis is part of more generalised allergic skin disease then management of the ear disease can often be achieved using systemic drugs or with allergen-specific immunotherapy. In some dogs, allergy only affects the ears, or affects the ears more severely than other areas. In other cases, systemic medication is inadequate in controlling allergic otitis and additional therapy is needed. In such situations topical drugs can be used as the sole source of therapy or can be used to supplement other modalities such as allergen-specific immunotherapy (Colombo *et al.* 2007). Treatment of secondary infection is important and will be dealt with under the appropriate sections below but the allergic reaction itself is best treated with anti-inflammatory therapy.

Topical anti-inflammatory therapy

Topical products containing either glucocorticoids (Rougier *et al.* 2005, Bolinder *et al.* 2006) or tacrolimus (Mauldin *et al.* 2007, Kelley *et al.* 2010) have been described as useful forms of anti-inflammatory therapy in dogs and cats for both allergic and immune-mediated disease. Licensed veterinary ear products containing glucocorticoids range from potent anti-inflammatory agents such as mometasone, hydrocortisone aceponate, fluocinolone, dexamethasone and betamethasone to moderately potent drugs such as triamcinolone acetonide and prednisolone (Koch *et al.* 2012). Almost without exception these glucocorticoids are found as components of compound products that also contain an antibiotic and an antiyeast drug. Glucocorticoid-only drops tend to be human products used off-license for dogs and cats. An exception is fluocinolone acetonide combined with dimethyl

Table 1. Primary causes of otitis externa

Primary trigger		Important qualities of topical therapy
Allergy	Atopy, food, contact	*Cleaning solutions* must be gentle in a sensitive ear. Acidic, alcohol-based, astringent solutions and potent ceruminolytics should be used with care. *Ear drops* containing glucocorticoids are useful. The potency of the glucocorticoid will depend on the degree of inflammation and the frequency of use. Topical products that can lead to contact allergy include propylene glycol and neomycin.
Endocrine	Hypothyroid	*Cleaning solutions* need to have good ceruminolytic activity in hypothyroidism when a ceruminous discharge is produced. Ceruminolytics such as squalene or sodium docusate may be used in the early stages of the disease but less potent wax removing agents should be used as the ear disease improves, e.g. oil and propylene glycol-based cleaners. *Ear drops* are often necessary to treat secondary yeast infection. Drops containing azoles, polyenes or allylamines (see text) are useful.
Autoimmune/immune mediated	Pemphigus foliaceus, bullous pemphigoid, discoid lupus erythematosus, erythema multiforme	*Cleaning solutions* must be gentle (as above) as the ear will be sensitive and often ulcerated. *Ear drops* need to contain a potent topical glucocorticoid, e.g. mometasone, hydrocortisone aceponate.
Keratinisation disorders	Sebaceous adenitis (SA), primary idiopathic seborrhoea (PIS)	*Cleaning solutions* in keratinisation disorders will depend on the amount of cerumen in the ear. In SA cerumen production is dramatically reduced so the ear canal is dry. Gentle oil-based should be used. In PIS potent dewaxing agents are needed such as carbamide peroxide, sodium docusate and squalene. *Ear drops* are often not as important as appropriate cleaning. Topical glucocorticoids may help in the management of PIS. Where secondary yeast infection is seen use drugs as above under endocrine disease.
Ectoparasites	*Otodectes cynotis*, *Demodex* species	*Cleaning solutions* must be able to break up the thick dried discharge seen in cases of *Otodectes cynotis*. Ceruminolytics products such as sodium docusate and squalene may be useful. More gentle cleaners are needed in cases of demodectic otitis, e.g. propylene glycol-based cleaners, *Ear drops* often have miticidal indications even though they do not contain a specific miticidal drug. Ear drops containing acaricides: avermectins, permethrin, thiabendazole, rotenone are useful.

Table 2. Secondary causes of otitis

Infection		Topical therapy
Bacteria	Gram-positive bacteria *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, *Corynebacterium* species Gram negative bacteria *Pseudomonas* species *Proteus* species, *Escherichia coli* Anaerobes	See appropriate section in text on suitable topical antibiotics and antibacterial ear cleaners
Yeast	*Malassezia* species	See appropriate section in text on suitable topical antiyeast drugs and cleansers

Table 3. Important predisposing factors in otitis

Predisposing factors		
Conformation	Hairy canals, stenotic canals, pendulous pinnae	Regular use of appropriate ceruminolytic/ceruminosolvent products (see text)
Excessive wetting of the ear canal	Environmental factors (heat and humidity); water (swimmers ear)	Regular use of topical drying agents can help manage swimmers ear
Obstructive ear disease	Neoplasia, polyps	Regular cleaning to remove discharge and control secondary infection is useful but not a long-term solution
Treatment effects	Inappropriate cleaning solutions, traumatic cleaning and plucking	Careful selection of cleaners is important to avoid acidic, potent ceruminolytic and astringent ear cleaners in sensitive ears. Regular cleaning is better than regular plucking

sulfoxide (DMSO). DMSO has many potential effects, but in this preparation specifically acts as a drug delivery system to carry the corticosteroid into the skin and is particularly suited to treating hyperplastic ear conditions. In an attempt to use a veterinary corticosteroid-based product to treat allergic otitis, a recent study demonstrated that off-license use of a spray containing hydrocortisone aceponate, at a dose of three drops twice weekly, into atopic dogs' ears, reduced the relapse rate of disease (Bensignor *et al*. 2012). Weak glucocorticoids such as 1% hydrocortisone are found in some countries as components of ear cleaning solutions where they are combined with other active ingredients such as Burow's solution, acetic acid, boric acid, ketoconazole and ethylenediamine tetra-acetic acid tromethamine (EDTA-Tris). The choice of an appropriate corticosteroid preparation should be based on a variety of factors, including the potency of the glucocorticoid that is required for therapy, the potency and concentration of the glucocorticoid in the topical preparation, the base that the glucocorticoid is in and the potential for systemic absorption of the drug relative to the animal's general health and the length of course that is needed. Two studies looking at the anti-inflammatory effects of glucocorticoids in otitis showed that topical prednisolone produced a significant reduction in ear thickness and erythema (Bolinder *et al*. 2006) but that when compared to dexamethasone, prednisolone was less effective in reducing pain,

Table 4. Important perpetuating factors in otitis

Perpetuating factors		
Pathological changes in the external ear canal	Inflammation in walls leading to loss of epithelial migration	Regular cleaning with appropriate ceruminolytic/ceruimosolvent ear cleaners to remove discharge. Appropriate use of potent topical corticosteroids to reduce swelling, hyperplastic change and cerumen production. Fluocinolone with DMSO is useful in some cases
	Inflammation of glandular tissue leading to narrowing of the canal and increased cerumen production	
Otitis media	Ruptured ear drum	Appropriate use of topical antibiotics and cleaners to treat infection but minimise risk of ototoxicity, n.b. all drugs in cases of otitis media are used off license
	Mucopurulent discharge due to inflammation of mucoperiosteum within bulla	Appropriate use of topical corticosteroids to reduce inflammation and discharge (see note above on ototoxicity and off license use of drugs)
	Biofilm formation within middle ear	Topical drugs may be useful to break down biofilm formation within the ear canal and middle ear

DMSO Dimethyl sulfoxide

Table 5. A review of veterinary studies assessing systemic absorption of otic glucocorticoids

Study	Health status of dogs	Study design (otic glucocorticoid and application)	Findings
Moriello *et al.* (1988)	Healthy	Dexamethasone or triamcinolone applied twice daily for 7 days according to manufacturer's instructions	ACTH response reduced in all dogs after 7 days. Recovery >21 days in all dogs
Meyer *et al.* (1990)	Healthy	Triamcinolone or dexamethasone both applied daily 3 weeks	Increase in liver enzyme test results after 7 days, peaked at 21 days. Recovery 35 days. Increases in dexamethasone group biggest
Ghubash *et al.* (2004)	Healthy small	Dexamethasone or betamethasone applied twice daily for 2 weeks according to manufacturer's instructions	ACTH performed after 2 weeks Betamethasone group NAD Dexamethasone group >70% depression of ACTH with 2-week recovery
Abraham *et al.* (2005)	Healthy	Dexamethasone twice daily for 21 days	ACTH performed days 7 and 14 of treatment suppressed in all dogs. Day 14 suppression>day 7. ACTH 7-days posttreatment still suppressed all dogs. Liver enzyme tests showed increases at days 7 and 14 and did not recover 7-days posttreatment
Reeder *et al.* (2008)	Otitis externa	Dexamethasone (twice a day) or mometasone (once a day) or betamethasone (twice a day) or triamcinolone (twice a day) (according to manufacturer's instructions) for 7 days	ACTH performed at 7 days. Mometasone NAD. Percentage of dogs with reduced ACTH response in other groups dexamethasone 50%, triamcinolone 17%, betamethasone 9%
Gottschalk *et al.* (2011)	Healthy	Dexamethasone applied daily for 3 weeks	Reduction in T4, T3, cortisol and increase in insulin at 21 day. Recovery of T4, T3>7 days

production of exudate, and odour (Rougier *et al.* 2005). Many different studies have shown that topical otic glucocorticoids can be absorbed systemically to affect both adrenal and hepatic function tests (Moriello *et al.* 1988, Meyer *et al.* 1990, Ghubash *et al.* 2004, Abraham *et al.* 2005, Reeder *et al.* 2008, Gottschalk *et al.* 2011). The study design and clinical finding for each investigation are outlined in Table 5. Findings in all studies in normal dogs showed that dexamethasone- and triamcinolone-based otic preparations cause suppression of the adrenocorticotropic hormone (ACTH) response, elevation in liver function tests and, for dexamethasone, suppression of thyroid function tests. Betamethasone appeared to produce fewer systemic affects than triamcinolone or dexamethasone (Ghubash *et al.* 2004, Reeder *et al.* 2008). Only a single study has considered the systemic absorption of topical glucocorticoids in ears with OE (Reeder *et al.* 2008). This study showed that no dogs showed signs of suppression of their ACTH response after 7 days of topical mometasone but that some dogs from the other treatment groups, betamethasone (9%), triamcinolone (17%) and dexamethasone (50%) did show suppression. The effect of the otic vehicle and glucocorticoid concentration on systemic absorption of glucocorticoid has also been assessed (Aniya & Griffin 2008). This study describes a comparison of dexamethasone at two concentrations (0·1 and 0·01%) and in two different vehicles (propylene glycol and saline). After 2 weeks of twice-daily application of topical glucocorticoid all dogs receiving dexamethasone 0·01% in saline had normal ACTH stimulation tests and liver enzyme levels but 57% of dogs receiving the 0·1% solution in saline had signs of adrenal suppression and 66% of dogs receiving dexamethasone in propylene glycol showed signs of adrenal suppression, which, in some cases, was marked. The study elegantly demonstrated that adrenal suppression caused by otic dexamethasone is concentration- and possibly vehicle-dependent. Two studies investigating the effects of otic glucocorticoids on intradermal skin testing showed that 2 weeks of topical betamethasone (Ginel *et al.* 2007) or mometasone (Marcia Murphy & Olivry 2015) suppressed intradermal reactions in laboratory beagles and dogs with atopic otitis, respectively. However, a withdrawal period of only 7 days was found

to be necessary for mometasone to allow recovery of intradermal reactivity (Marcia Murphy & Olivry 2015). Tacrolimus is a macrolide lactone drug labelled for use in people with moderate to severe atopic dermatitis. Recently tacrolimus ointment has been found to be effective in treating refractory non-infectious otitis in people (Caffier *et al.* 2007, Harth *et al.* 2007, Lennon & Fenton 2010). There are limited reports of its use in dogs and cats. One report has shown when a sterile olive oil-based 0·1% tacrolimus suspension was used in the ears of atopic beagles without OE that it produced no signs of adverse local reactions, development of OE, change in otic cytology, vestibular dysfunction or hearing loss (Kelley *et al.* 2010). Topical 0·1% tacrolimus has also been used successfully to treat proliferative necrotising otitis in three adult cats (Mauldin *et al.* 2007).

Topical acaricidal drugs

A number of different liquid aural preparations are licensed for the topical treatment of *Otodectes cynotis* in dogs and cats (Curtis 2004). Most products contain a recognised acaracide but a number of non-acaricidal products have been shown to be effective (Pott & Riley 1979, Scherk-Nixon *et al.* 1997, Engelen & Anthonissens 2000). These three studies investigated the efficacy of two different oil-based ear drops to kill *O. cynotis*. One product contained miconazole, polymyxin and prednisolone and the other contained diethanolamine fusidate, framycetin, nystatin and prednisolone. Both products were found to be highly effective. The authors of the reports concluded that although some of the component of the ear drops may have unknown acaricidal activities it was more likely that it was the oil base that created an incompatible environment in the ear for mite survival. Acaricides in licensed veterinary ear drops include ivermectin, milbemycin, monosulfiram, permethrin, piperonyl butoxide, pyrethrins and rotenone (Koch *et al.* 2012). With the exception of the avermectins (ivermectin, milbemycin) these drugs have a limited residual action and require regular re-application for at least 10 days, to ensure that all ova have hatched and that the newly emerged larvae are exposed to the drug (Curtis 2004). Thiabendazole has been shown to be effective in eliminating *O. cynotis* in dogs when used at a dose of 50 mg per ear for 7 days (De Souza *et al.* 2006) and has been shown to be effective as therapy when combined with dexamethasone and neomycin (Faulk & Schwirck 1978). An auricular ointment containing 10 mg/g of permethrin was shown to be an effective treatment for *O. cynotis* in cats in two studies (Roy *et al.* 2011, 2012). In the second study, it was found to be superior, in its improvements of clinical signs of OE, to a selamectin spot-on preparation (Roy *et al.* 2012). Off-licence use of topical ivermectin (Huang & Lien 2000), fipronil (Vincenzi & Genchi 1997) and pyriproxyfen (Bourdeau & Cohen 2000) have also been described. A 1% ivermectin solution diluted 1:9 with propylene glycol was administered daily for 21 days to 32 affected cats. A complete response to therapy without any adverse reactions was recorded (Huang & Lien 2000). In another study involving 35 dogs and 14 cats a single otic application of two drops of 10% solution of fipronil was effective in controlling *O. cynotis* without any adverse effects. A third study used four drops of a 10% solution of pyriproxyfen to a single ear of eight affected cats. Although the product controlled the mites it failed to prevent re-infestation at day 60 (Bourdeau & Cohen 2000). Demodectic OE is an uncommon primary trigger for ear disease. There are few reports in the literature of topical treatment protocols. Some authors have suggested similar treatment regimens with ivermectin to those used for *O. cynotis* (Rosychuk 1994). Other authors have suggested a mixture of amitraz at a concentration of 0·13% (Muller 1983) or 0·5% (Knottenbelt 1994) in liquid paraffin or mineral oil, applied topically every 3 days.

TOPICAL THERAPY TO MANAGE SECONDARY CAUSES OF OTITIS

Infection is always secondary in cases of OE. Both bacterial and yeast infection can occur as a result of the inflammatory process created by the primary disease. Numerous papers have reported antibacterial and antiyeast activity of both ear cleaners and ear drops.

Topical products with antiyeast activity

Licensed veterinary products with medicinal claims to treat *Malassezia*, the most important yeast found in cases of otitis, contain either polyenes, azoles or allylamines. Most of these antiyeast drugs are combined with a corticosteroid and an antibiotic to form compound ear drops (Koch *et al.* 2012). The exception is a few veterinary products that contain only clotrimazole (1%) or miconazole (1%) (Koch *et al.* 2012). Nystatin is the principal polyene antifungal found in veterinary ear drops. It works by binding to sterols in the fungal cell membrane, leading to changes in permeability and fungal death due to osmotic destruction. Nystatin is available as a combination ear product in both Europe and America. In Europe it is combined with framycetin, prednisolone and fusidic acid, in America it is combined with triamcinolone acetonide, neomycin and thiostepton. Azole antifungal drugs disrupt the biosynthesis of the ergosterol in the fungal cell wall. Topical azoles are available in ear products as imidazoles (clotrimazole, miconazole, ketoconazole) or triazoles (itraconazole, posaconazole). All of the azoles have excellent in vitro activity against *Malassezia* species (Schmidt 1997, Hensel *et al.* 2009, Pietschmann *et al.* 2013, Chiavassa *et al.* 2014). Several studies which have used different methodologies have tried to establish the relative potency of the different azoles. One study suggested that itraconazole was the most potent followed by ketoconazole, miconazole and clotrimazole (Lorenzini *et al.* 1985). However, another in vitro study suggested ketoconazole, itraconazole and terbinafine were equipotent (Gupta *et al.* 2000). More recently a comparison of miconazole and clotrimazole suggested miconazole was the more potent (Peano *et al.* 2012). The triazole posaconazole was found to be more effective than three other antifungal drugs: miconazole, clotrimazole and nystatin when used to treat *Malassezia* infection in dogs (Bordeau *et al.* 2004). A study looking at a product combining marbofloxacin, clotrimazole and dexamethasone showed that although drops consisting of miconazole only treated the *Malassezia* as well as the combined drops, the dexamethasone-based product reduced signs of erythema, pruritus and wax production more effec-

tively (Bensignor & Grandemange 2006). Allylamines disrupt ergosterol biosynthesis and prevent fungal cell wall formation. Terbinafine is the most widely used product in this class and has recently become available as a long acting veterinary ear drop combined with betamethasone and florfenicol, licensed for once weekly aural application for two consecutive weeks per month. In America there is long-acting product containing florfenicol, terbinafine and mometasone which is licensed for once-monthly application. Many different antiseptic ear cleaners have been shown in vitro to have antiyeast activity. Several studies have looked at the in vitro activity of ear cleaning solutions against *Malassezia pachydermatis* (Lloyd *et al*. 1998, Lloyd & Lamport 2000, Swinney *et al*. 2008, Guardabassi *et al*. 2010, Mason *et al*. 2013). Whilst it is difficult to conclude the exact reason for the extent of in vitro activity of the ear cleaners tested because they varied widely in their ingredients, there are components of many of them with proven antiyeast activity. Ketoconazole as an azole has good activity against *Malassezia* reinforced by two ear cleaner studies (Cole *et al*. 2007, Mason *et al*. 2013). Parachlorometaxylenol (PCMX), a component of many ear cleaners, is also suggested to confer antiyeast activity (Lloyd & Lamport 2000, Reme *et al*. 2006, Cole *et al*. 2007, Swinney *et al*. 2008). All of the cleaners in Mason's study (Mason *et al*. 2013) that contained PCMX had excellent or good anti-*Malassezia* activity. Isopropyl alcohol and propylene glycol (Larson & Morton 1991) may also provide antimicrobial benefits. Organic acids such as lactic acid, salicylic acid, acetic acid, boric acid, oleic acid and citric acid are ingredients in many of the cleaners showing good antiyeast activity. Of these acids, salicylic (Wilke 1988) and boric acid (Bassett *et al*. 2004, Mendelsohn *et al*. 2005) have been shown to have good antiyeast activity. Chlorhexidine at a concentration of 2 to 4% is an antiseptic with good activity against *Malassezia* as demonstrated by several shampoo studies (Bond *et al*. 1995, Lloyd & Lamport 1999, Young *et al*. 2012). However, the low concentration of chlorhexidine in ear cleaners (0·15%) may reduce its anti-*Malassezia* action (Guardabassi *et al*. 2010).

Topical antibiotic products

There are numerous ear products containing antibiotics or disinfectants with antibacterial activity. The most common topical antibiotics are aminoglycosides (framycetin, gentamicin, neomycin); fluoroquinolones (ciprofloxacin, enrofloxacin, marbofloxacin, orbifloxacin); polymyxins (colistin sulphate, polymyxin B) fusidic acid, florfenicol and silver sulphadiazine (Koch *et al*. 2012).

Fusidic acid

Fusidic acid is a narrow spectrum bacteriostatic antimicrobial. Its principal mode of action is as an anti-staphylococcal antibiotic and has been shown to be useful against methicillin-resistant strains of staphylococcus (Verbist 1990). It also has good activity against *Corynebacterium* species, which is now recognised as a significant aural pathogen (Aalbaek *et al*. 2010) and anaerobes. It is an excellent empirical first choice for staphylococcal infections (Harvey & Paterson 2014a) and is found in a combination product with framycetin, prednisolone and nystatin in Europe.

Aminoglycosides

Aminoglycoside antibiotics are bactericidal and act on susceptible bacteria by binding to the 30s ribosomal subunit in the bacterial nucleus thereby inhibiting protein synthesis. Framycetin, neomycin and gentamicin are all found in licensed veterinary ear drops. Framycetin is a broad spectrum bactericidal drug with good activity against *Staphylococcus* species. It has been shown to be synergistic when used in vitro with fusidic acid (Allison *et al*. 2011). It also has good activity against many Gram-negative pathogens including *Proteus* species and some strains of *Pseudomonas* species (Harvey & Paterson 2014a). Framycetin is available in Europe as a combination product with fusidic acid, prednisolone and nystatin. Neomycin is the least potent of the veterinary aminoglycosides. It has good activity against Gram-positive cocci but only very limited activity against Gram-negative bacteria. It is often recommended as a good first-line drug when cocci are found on otic cytology (Morris 2004). Synergistic activity has been observed when EDTA-Tris plus neomycin were tested against *Staphylococcus pseudintermedius*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Escherichia coli* (Sparks *et al*. 1994). Neomycin is reported to be a common aural contact sensitizer in dogs (Rosychuk 1994), it is also recognised in humans as the most common topical antibiotic to cause contact allergy (Holmes *et al*. 1982, Van Ginkel *et al*. 1995, Hillen *et al*. 2000, Millard & Orton 2004). The most recent of these publications showed that all neomycin-allergic patients are also allergic to framycetin and gentamicin (Millard & Orton 2004). If the same is true in dogs, switching to another aminoglycoside is probably unwise if a reaction is seen to neomycin. Neomycin is found in four different topical products these are in combination with (1) hydrocortisone and polymyxin B; (2) triamcinolone acetonide, nystatin and thiostrepton; (3) isoflupredone, tetracaine hydrochloride and (4) dexamethasone with thiabendazole (Koch *et al*. 2012). Gentamicin has a good range of activity against both Gram-positive and Gram-negative bacteria. Numerous clinical studies have shown activity against *Staphylococcus* species (Kiss *et al*. 1997, Lyskova *et al*. 2007, Zamankhan Malayeri *et al*. 2010); as well as *Corynebacterium* species (Henneveld *et al*. 2012); *Proteus* species, *E. coli* (Lyskova *et al*. 2007, Zamankhan Malayeri *et al*. 2010, Bugden 2013) and *Pseudomonas* species (Kiss *et al*. 1997, Lyskova *et al*. 2007, Schick *et al*. 2007, Zamankhan Malayeri *et al*. 2010, Bugden 2013). A wide range of veterinary commercial products are available containing gentamicin combined with a corticosteroid and, usually, an antifungal drug. Combinations include with betamethasone; mometasone furoate and clotrimazole; betamethasone and clotrimazole and hydrocortisone aceponate and miconazole (Koch *et al*. 2012). Other aminoglycosides that have been used as extra-label products include amikacin and tobramycin (Morris 2004). Amikacin and tobramycin should, in the opinion of the author, only be used when dictated by culture and sensitivity and only when other drugs are unsuitable. Amikacin has excellent activity against Gram-positive otic pathogens *Staphylococcus* species (Zamankhan Malayeri *et al*. 2010) and *Corynebacterium* species (Henneveld *et al*. 2012). It also has excellent activity against Gram-negative organisms

Pseudomonas species (Schick *et al*. 2007, Zamankhan Malayeri *et al*. 2010). Injectable formulations of amikacin can be used as an off licence product diluted to a concentration of 30 to 50 mg/mL in sterile saline or EDTA-Tris (Morris 2004). Synergistic activity has been observed when EDTA-Tris plus amikacin were tested against *S. pseudintermedius*, *P. mirabilis*, *P. aeruginosa* and *E. coli* (Sparks *et al*. 1994). Tobramycin is available as ophthalmic drops for human therapy which can be used extra-label in the ears of dogs and cats (Morris 2004, Koch *et al*. 2012). Injectable solutions may be mixed with sterile saline or EDTA-Tris to concentrations of 8 mg/mL for otic use (Morris 2004). The long-term stability of tobramycin and amikacin solution made up for off-licence usage is unknown. Both antibiotics are potentially ototoxic (Harvey & Paterson 2014a).

Fluoroquinolones

Fluoroquinolones are bactericidal antibiotics that act by inhibiting bacterial DNA gyrase which prevents DNA supercoiling and synthesis. They have good activity against a wide range of bacteria, especially Gram-negative bacilli and Gram-positive rods (including *Staphylococcus* species but with variable activity against *Streptococcus* species (McKellar 1996). Ciprofloxacin, enrofloxacin, marbofloxacin and orbifloxacin have all been shown to have good activity against *Pseudomonas* species in cases of OE (Rougier *et al*. 2005, Schick *et al*. 2007, Wildermuth *et al*. 2007, Zamankhan Malayeri *et al*. 2010) which has led to the widespread use of these drugs as second or third line antibiotics in chronic, recurrent otitis especially in cases associated with *P. aeruginosa*. Unfortunately as a result of this increased usage, resistance of *Pseudomonas* species to fluoroquinolones is being reported more commonly (Martin Barrasa *et al*. 2000) and some studies have shown very high rates of resistance, in one case up to 87·5% of *Pseudomonas* species strains were not susceptible to enrofloxacin (Cole *et al*. 1998). Enrofloxacin is available as a veterinary ear drop combined with silver sulphadiazine in the USA (Koch *et al*. 2012). Marbofloxacin and orbifloxacin are widely available as otic drops. In some countries they are only obtainable under limited licence to restrict their usage. Veterinary products are available containing marbofloxacin combined with dexamethasone and clotrimazole and orbifloxacin combined with posaconazole and mometasone. Off-licence use of injectable fluoroquinolones mixed with sterile saline or EDTA-Tris have been employed where licensed veterinary products are not available or where they are deemed unsafe due to damage to the tympanic membrane (see section on otitis media). Injectable 2% enrofloxacin diluted 1:6 in water has been recommended (Farca *et al*. 1997). Other dilutions include a 1:3 dilution of 2% enrofloxacin or 1% marbofloxacin mixed with EDTA-Tris (Paterson 2012). A study investigating the stability of 0·9% enrofloxacin made up in different solutions, showed it had good chemical stability and antibacterial activity for 28 days made up in (1) sterile water; (2) EDTA-Tris ear cleaner (with and without 0·15% chlorhexidine); (3) 0·1% salicylic acid and 0·1% parachlorometaxlenol (with either 2·5% lactic acid or 0·5% EDTA) (Metry *et al*. 2012). When ciprofloxacin is prescribed it is generally as extra-label usage of a human ophthalmic solution (Koch *et al*. 2012).

Polymyxins

Polymyxin B and colistin sulphate are polypeptide antibiotics that exert bactericidal effects by increasing permeability of the bacterial cell membrane via chelation of membrane phospholipid components leading to osmotic damage (Morris 2004). Polymyxins have excellent activity against most Gram-negative bacilli (Kiss *et al*. 1997, Gales *et al*. 2006, 2011). They appear to be less effective against Gram-positive bacteria (Bugden 2013) unless combined with miconazole (Pietschmann *et al*. 2013). Polymyxin B is widely available as a veterinary preparation combined with prednisolone and miconazole. Several veterinary publications have considered this product: an early Australian study demonstrated that it was superior to two different neomycin-corticosteroid preparations when relapse rates were considered for cases of otitis (Studdert & Hughes 1991). More recent reports have shown that there is marked synergy of the two products for Gram-negative infection with *E. coli* and *Pseudomonas* species (Pietschmann *et al*. 2013) and although there was no demonstrable synergy the combination product also had good activity against methicillin-resistant *Staphylococcus* species (Boyen *et al*. 2012). A marbofloxacin, dexamethasone, clotrimazole veterinary preparation has been shown to be equivalent in its antibacterial and antiyeast activity to a polymyxin, miconazole, prednisolone product but superior in regard to pain relief and decrease in pus quantity and smell (Rougier *et al*. 2005). These benefits may be attributed to the dexamethasone, a more potent corticosteroid in the comparative product. Colistin sulphate is not available as a veterinary preparation but extra-label use of human otic products is advocated by some clinicians (Morris 2004).

Silver sulphadiazine

Silver exerts its antibacterial effects via impairment of DNA replication and bacterial cell wall damage, leading to osmotic change (Hoffmann 1984). The spectrum of activity of silver sulphadiazine includes many of the pathogens associated with otitis including methicillin-resistant strains of *Staphylococci* and *Pseudomonas* species (Bogaard Van Den & Bohm 1986). A veterinary product containing 1% silver sulphadiazine with 0·5% enrofloxacin is available in the USA (Koch *et al*. 2012). Where silver sulphadiazine is not available as proprietary veterinary products 1% silver sulphadiazine cream can be diluted in EDTA-Tris. A recent study has shown that EDTA-Tris potentiates the activity of silver sulphadiazine against resistant strains of *P. aeruginosa* (Buckley *et al*. 2012). A further study has shown that even if the cream is diluted 1 in 100 it will still exceed the MIC for *P. aeruginosa* when applied to the ear canal (Noxon *et al*. 1997).

Florfenicol

Florfenicol is a bacteriostatic antibiotic that works by inhibiting protein synthesis. Its spectrum of activity is similar to chloramphenicol. It has been shown to have good activity against Gram-positive bacteria *Staphylococcus* species and Gram-negative

bacteria *Proteus* species and *Enterococcus* species. It has very limited activity against *Pseudomonas* species. A retrospective study looking at the susceptibility of *Corynebacterium* species to a range of different antibiotics showed chloramphenicol had excellent activity against *Corynebacterium* species (Henneveld *et al.* 2012). It can be assumed that florfenicol will have similar efficacy. Florfenicol is available in two different long acting topical otic products. In one it is combined with betamethasone and terbinafine to be applied once a week for two consecutive weeks each month; in the other it is combined with terbinafine and mometasone for once monthly application.

Other antibiotics

Ticarcillin has been described as a useful therapy for OE complicated by *P. aeruginosa* (Nuttall 1998). The protocol described by Nuttall in his paper suggests that a 6-g vial of ticarcillin is mixed with 12 mL of sterile diluent. This may be divided into 2 mL aliquots and frozen. The vials can be thawed and mixed with 40 mL of sterile saline which can be then frozen in 10 mL amounts to be thawed and used as needed. The stability and efficacy of the ticarcillin used in this way was investigated in a further study (Bateman *et al.* 2012). This work indicated that storage of the ticarcillin stock solution at −20°C does not compromise efficacy for at least 12 months. In addition, the ticarcillin diluted in carrier vehicle Methopt remained stable for 28 days when stored at 4 or 24°C. Although ticarcillin is a useful drug for the therapy of multiply-resistant bacterial isolates its use should be reserved for cases where sensitivity has been undertaken and no other drug is deemed suitable. It should also be used with care if the ear drum is ruptured (Harvey & Paterson 2014a). Ticarcillin is unavailable in commercial products in America.

Topical ear cleaners with antibacterial activity

Many different ear cleaning solutions have been shown to have antibacterial activity (Blue *et al.* 1974, Wooley & Jones 1983, Lloyd *et al.* 1998, Lloyd & Lamport 2000, Cole *et al.* 2003, 2007, Reme *et al.* 2006, Swinney *et al.* 2008, Guardabassi *et al.* 2010, Bouassiba *et al.* 2012, Steen & Paterson 2012). Antimicrobial activity of topical products may be due to the active ingredients or in some cases it is thought it may be due to the pH of the solution. One study (Swinney *et al.* 2008) suggested that ear cleaning solutions with a low pH were likely to have good antimicrobial properties. However, a more recent study (Steen & Paterson 2012) identified an ear cleaning solution with a pH of 2·8 which had no antibacterial activity against *Pseudomonas* species suggesting that the acidity of a solution is not as important as once thought. Isopropyl alcohol (IPA) is known to have excellent antibacterial properties (Larson & Morton 1991), is a common component of many ear cleaning solutions and is thought to contribute to the antibacterial properties of some products (Swinney *et al.* 2008). Monosaccharides in ear cleaning solutions act as microbial adhesion-blocking carbohydrates and have been shown to have antibacterial effects (Reme *et al.* 2006). PCMX is a broad spectrum phenolic germicide that has antibacterial properties (Steen & Paterson 2012). Although it may have activity against Gram-positive organisms (Swinney *et al.* 2008), it has an inconsistent activity in vitro against *Pseudomonas* species (Steen & Paterson 2012). Organic acids such as acetic acid, citric acid, lactic acid and salicylic acid are ingredients in many of the cleaners showing good antibacterial activity. Acetic acid is known to have good activity against a wide range of bacteria (Thorp *et al.* 1998, Van Balen *et al.* 2003). One study showed that 2 and 3% acetic acid used to treat otitis in humans had good in vitro activity against *P. aeruginosa*, *Staphylococcus aureus* and *P. mirabilis*. The anti-pseudomonas effect of acetic acid has been demonstrated in several subsequent veterinary studies (Bussieras *et al.* 1998, Cochat-Aubert 1998, Steen & Paterson 2012). Citric acid has also been shown to have anti-pseudomonas activity (Strauss *et al.* 2005). Lactic acid is known to disrupt the outer cell membrane of Gram-negative bacteria (Alakomi *et al.* 2000). Several studies have shown that lactic acid, which is typically used at a concentration of 2·5% in veterinary ear cleaners, has excellent in vitro activity against not only *Pseudomonas* species (Steen & Paterson 2012) but also Gram-positive bacteria such as *Staphylococcus* species (Lloyd *et al.* 1998, Lloyd & Lamport 2000, Cole *et al.* 2003, Swinney *et al.* 2008). Burow's solution, an aqueous solution of aluminium acetate, is topical product used commonly in the USA. It is found as a component of ear cleaning solutions. Although it has not been the subject of any veterinary trials it has been recognised for some time as an effective antibacterial therapy against *Pseudomonas* species, *Staphylococcus* species and *Proteus* species for otitis in people (Thorp *et al.* 1998, Hyo *et al.* 2012). Chlorhexidine at a concentration of 0·15% is found in several European and American ear cleaning products and has good activity against both Gram-positive and Gram-negative organisms (Swinney *et al.* 2008, Guardabassi *et al.* 2010, Steen & Paterson 2012). Hypochlorous acid is a broad spectrum antimicrobial with a rapid action against Gram-positive and Gram-negative bacteria (Koch *et al.* 2012). Its bactericidal action relies on disruption of the bacterial cell membrane (Hidalgo *et al.* 2002). EDTA-Tris is an antimicrobial product that works by blocking the *Pseudomonas* efflux pump; disrupting the cell walls of Gram-negative bacteria by chelating metal ions and rendering the bacterial cell more porous and by inhibiting the effects of ulcerating bacterial enzymes (Blue *et al.* 1974, Wooley & Jones 1983, Foster & Deboer 1998, Koch *et al.* 2012). Despite its mode of action, recent in vitro studies have shown that EDTA-Tris has, at best, weak antibacterial properties (Swinney *et al.* 2008, Metry *et al.* 2012, Steen & Paterson 2012) but has excellent antibiotic- and antiseptic-potentiating activity. Used as an otic flush 15 to 20 minutes prior to the addition of other antimicrobials it has strong potentiating effects with chlorhexidine (Guardabassi *et al.* 2010), silver sulphadiazine (Buckley *et al.* 2012), aminoglycosides (Sparks *et al.* 1994, Buckley *et al.* 2013), fluoroquinolones (Farca *et al.* 1997, Ghibaudo *et al.* 2004, Buckley *et al.* 2013) and chloramphenicol (Farca *et al.* 1991). One study investigating an ear-rinse containing EDTA-Tris and benzoyl alcohol showed that this product had good in vitro antibacterial activity, although the authors suggested that it may be the alcohol rather than the EDTA-Tris that produced the antibacterial effects (Cole *et al.* 2006).

Other topical products with antibacterial activity

Natural topical products have been investigated as potential alternatives to antibiotics. Most of the studies are in vitro and are not blinded or placebo-controlled, so all data should be interpreted with this knowledge. Propolis or bee glue is a resinous substance that honey bees collect from tree buds and sap flowers. One study found it had antimicrobial properties against both coagulase positive *Staphylococcus* species and *M. pachydermatis* from cases of OE (Cardoso *et al.* 2010). Beta-thujaplicin is an organic compound found in the essential oil of the Pacific red cedar tree. An in vitro investigation showed that it had activity against *M. pachydermatis* (Nakano *et al.* 2005). An ethyl acetate leaf extract of *Harungana madagascariensis* Lam. Ex Poir (Hypericaceae) was assessed for activity against otic pathogens *M. pachydermatis*, *S. pseudintermedius* and *Pseudomonas* species. Results from the study suggest that the extract could be used as an antimicrobial preparation for OE (Moulari *et al.* 2007). A recent open pilot study considered the efficacy of medical grade honey (MGH) in the management of canine OE. In vitro assays of the biocidal activity of MGH showed activity against all bacterial isolates including methicillin-resistant *S. pseudintermedius*. Dogs with otitis were prescribed MGH (1·0 mL daily per ear) until cure was achieved for a maximum of 21 days. Dogs were scored on the basis of swelling, erosion/ulceration and exudate to a maximum of 12. Dogs were deemed to be clinically cured if the score was reduced to 3 or below. On this basis 90% of dogs achieved a clinical cure at 21 days, although not all of them were cytologically normal at this time (Maruhashi *et al.* 2016).

TOPICAL THERAPY TO MANAGE PREDISPOSING FACTORS

Although predisposing factors do not cause otitis they need to be managed to promote resolution of disease and prevent recurrence of the problem. Conformation and environmental factors are some of the most important predisposing factors, together with inappropriate treatment choices. Although many of the veterinary ear cleaners have excellent antibacterial and antiyeast activity, their ability to effective clean and dry the ear is often overlooked. Hairy ear canals, stenotic ear canals and dogs with pendulous ears need to have their ears cleaned effectively. Where animals with predisposing conformational problems such as these have primary triggers such as allergy causing inflammation within the ear canal, the prudent use of antibacterial ear flushes can help reduce the risk of secondary infection. Effective ear cleaning is also important in to remove wax to allow penetration of other drugs and to be able to assess the integrity of the tympanic membrane.

Ceruminolytic ear cleaners

The ability to effective clean ears to remove wax is an important part of the treatment and then ongoing maintenance therapy for otitis. True ceruminolytics ear cleaners disrupt the integrity of cerumen by inducing lysis of the squames (Robinson *et al.* 1989). They emulsify debris breaking it up and keep it in solution (Nuttall & Cole 2004). Diocytl sodium sulphosuccinate (DOSS), calcium sulphosuccinate, urea or carbamide peroxide are potent ceruminolytics. Urea and carbamide peroxide are foaming agents that release oxygen in situ to help break up debris. There are numerous American and European ear cleaners that contain these ingredients (Nuttall & Cole 2004). Ceruminosolvent ear cleaners are organic oils and solvents that soften and loosen cerumen. Examples of these are butylated hydroxytoluene, cocamidopropyl betaine, glycerine, lanolin, propylene glycol and squalene (Nuttall & Cole 2004). Squalene is the most potent of these wax-removing agents and is found in several veterinary ear cleaners. Some cleaners have it present at low concentrations of 2% whilst other more potent ceruminosolvent cleaners have squalene at concentrations of 22 to 25% (Koch *et al.* 2012). A synthetic canine cerumen has been designed and used, in slightly varying formulations, in several studies to look at the ceruminolytic properties of different ear cleaners (Nielloud *et al.* 2004, Sanchez-Leal *et al.* 2006, Robson *et al.* 2009). In all cases, antiseptic ear cleaning solutions that contained components such as chlorhexidine, without a recognised ceruminolytic, showed a poor ability to remove wax. However, propylene glycol, glycerine and squalene-based products consistently performed well. In one study (Sanchez-Leal *et al.* 2006), a propylene glycol and glycerine ear cleaner appeared to be able to remove 90% of the synthetic cerumen from a test tube. No urea or carbamide peroxide cleaners were tested but cleaners containing DOSS appeared to be less successful at wax removal in these three in vitro studies. The author would generally recommend the use of a suitable ceruminolytic/ceruminosolvent cleaner for dogs with hirsute ears rather than plucking out the hair, which can cause microtrauma in the ear canal and predispose to infection.

Drying ear cleaners

Astringents dry the ear canal surface to prevent maceration (Nuttall & Cole 2004). Drying agents are typically used after the ear has been cleaned with a ceruminolytic/ceruminosolvent product or are used prophylactically after water is introduced into the ear canal either by aqueous-based treatments, bathing or swimming (Koch *et al.* 2012). Astringents are usually isopropyl alcohol or an acid. Acids found in ear cleaners for this purpose include acetic acid, boric acid, benzoic acid and salicylic acid as well as aluminium acetate and silicon dioxide (Nuttall & Cole 2004). In the USA, there are many different ear cleaning solutions designed specifically for their antiseptic astringent effects. In Europe drying agents are often incorporated into more general ear cleaning products.

TOPICAL THERAPY TO MANAGE PERPETUATING FACTORS

Management of perpetuating factors is important to facilitate resolution of otitis. Chronic change is often inadequately addressed in cases of otitis and is a common reason for disease relapse. Where there is marked hyperplastic change of the walls of the canal and/or the glandular tissue within the wall, potent steroid

treatment is needed to reverse these changes. A full discussion on the management of chronic changes in otitis is beyond the scope of this article. Some of the liquid bandages, ear packs and other "stay in place" otics, together with topical corticosteroids in ear drops, in aqueous solution in ear wicks or systemic corticosteroids are useful (Harvey & Paterson 2014a). OM is a common sequel to chronic OE and is another perpetuating factor that needs to be treated. Selection of topical therapy for cases of OM can be challenging because of the risk of ototoxicity. No topical products are licensed for the therapy of OM, so it is important that the attending clinician should select the safest possible product available (which may sometimes be a systemic drug) based on current knowledge. For a detailed description of the clinical signs and diagnosis of OM the reader is advised to consult more detailed texts (Gotthelf 2004, Harvey & Paterson 2014b). Propylene glycol is a solvent and penetration enhancer and is a common component of many different ear drops and cleaners. It has been shown in experimental studies to be ototoxic when instilled into the middle ear (Morozono 1988, Little *et al*. 1991). Ear drops and cleaners containing propylene glycol should therefore be used with care if the ear drum cannot be seen. A study looking at four commercial ear cleaning solutions containing squalene, DOSS, carbamide peroxide and triethanolamine instilled into canine ears showed only the ear cleaner containing squalene produced no morphological or neurological changes (Mansfield *et al*. 1997). Antiseptic solutions show differing degrees of ototoxicity. Alcohol-based preparation of iodine and povidone iodine applied to the middle ear of guinea pigs produced cochlear and vestibular damage whereas aqueous solution of iodine produced no damage (Aursnes 1982). Chlorhexidine at concentrations up to 0·2% appears to be safe as an irrigating solution in dogs (Merchant 1994). However, when combined with cetrimide in a commercial human antiseptic, it is ototoxic (Galle & Venker-Van Haagen 1986). In cats' ears, solutions of chlorhexidine as dilute as 0·05% appear to cause cochlear, vestibular and mucosal damage (Igarashi & Suzuki 1985, Igarashi & Oka 1988a,b). Ear cleaners containing chlorhexidine should therefore be avoided in cats. Anecdotal reports suggest that a 2 to 2·5% solution of acetic acid solution is safe in the face of a ruptured tympanic membrane (Rosychuk 1994). EDTA-Tris is a common component of many different otic cleaners, including several products where it is available as crystals to be reconstituted with sterile water (Nuttall & Cole 2004). It has been widely promoted by many different sources as a safe and efficacious therapy, especially when combined with aqueous antibiotics, for Gram-negative OM (Farca *et al*. 1997, Kiss *et al*. 1997, Foster & Deboer 1998, Paterson 2012). Many of the studies assessing the ototoxicity of antibiotics have been performed in guinea pigs and chinchillas and extrapolation of data between species can be misleading. Canine studies to assess the use of gentamicin in OM have shown no noticeable degree of cochlear or vestibular ototoxicity (Strain *et al*. 1995, Paterson & Payne 2008). Other topical aminoglycosides such as tobramycin, as well as the semi-synthetic penicillin ticarcillin, have been associated with severe hearing loss when used to treat OM (Paterson & Payne 2008). Aqueous solutions of fluoroquinolones including enrofloxacin and marbofloxacin appear to be safe when used in the canine middle ear (Paterson & Payne 2008, Paterson 2012). Conflicting information appears to be available regarding the use of topical azoles in cases of OM. Although some veterinarians consider antifungal drugs such as clotrimazole, miconazole, nystatin and tolnaftate safe in cases of OM based on studies in guinea pigs (Tom 2000), the author has seen numerous cases of temporary deafness associated with ear drops containing clotrimazole and miconazole. Although this may be associated with other components of the drops she would caution against such products in cases of OM. Aqueous forms of dexamethasone and fluocinolone appear to be safe in the middle ear (Paterson & Payne 2008, Harvey & Paterson 2014b).

Conflict of interest

The author is a veterinary consultant to Dechra and ICF and has in the past 5 years received fees or reimbursement from Bayer, CEVA, Elanco, Zoetis.

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