Successful management of otitis externa

General approach to chronic or recurrent otitis and the best management steps are discussed by Tom Nuttall BSc BVSc CertVD PhD CBiol MSB MRCVS, RCVS specialist in veterinary dermatology, Royal (Dick) School of Veterinary Studies in Edinburgh, Scotland

Most cases of otitis externa can be clinically divided into erythroceruminous or suppurative otitis (see Figure 1). Erythroceruminous otitis is characterised by erythema, pruritus and a ceruminous to seborrhoeic discharge. It is most commonly associated with a Staphylococcal or *Malassezia* overgrowth. Suppurative otitis is characterised by erythema, ulceration, pain and a purulent discharge. Most cases are associated with a *Pseudomonas* species infection. Cytology can be used to quickly confirm the presence of Otodectes mites, neutrophils, staphylococci, other cocci, rods and *Malassezia*.

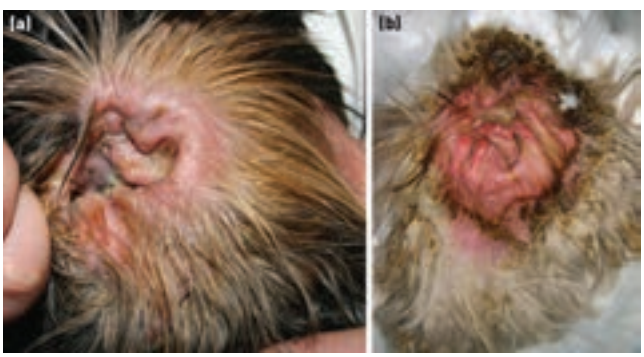


Figure 1: Erythroceruminous (a) and suppurative otitis (b). Erythroceruminous otitis is characterised by erythema, pruritus and a waxy to seborrhoeic discharge. Most cases are associated with staphylococci or *Malassezia* species and neutrophils are rare. Suppurative ears are often painful and ulcerated with a neutrophil-rich purulent discharge. Most cases are associated with *Pseudomonas* species.

Otoscopy is important to determine the state of the ear canals, the type and amount of discharge and the integrity of the tympanic membrane. All cases of acute otitis should be carefully examined to rule out foreign bodies and Otodectes mites.

UNDERLYING CAUSES

Chronic or recurrent otitis should be carefully evaluated to identify primary, predisposing and perpetuating causes. Successful management requires that these are all treated. The goals are:

- Identify and manage the primary cause;
- Correct predisposing factors (if possible);
- Remove debris and discharge;
- Manage the secondary infection; and
- Reverse chronic pathological changes.

BIOFILMS

Biofilms have a major impact on treatment and antimicrobial resistance. They are common and under-diagnosed, although they can be easily identified on otoscopy or cytology. Clinically, they form an adherent, thick and slimy discharge that is often dark brown or black (see Figure 2). On cytology, they appear as variably thick veil-like material that may obscure bacteria and cells (see Figure 3).

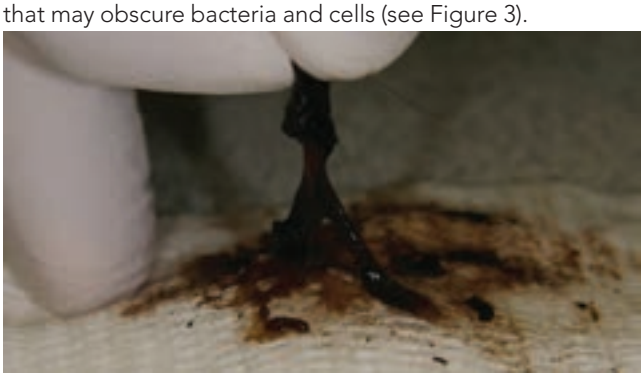
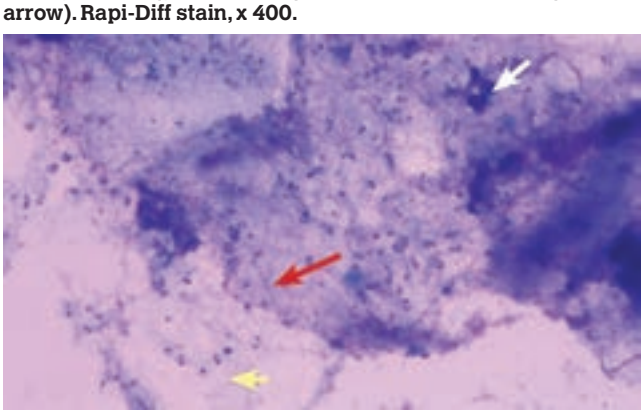


Figure 2: Biofilm from a dog with otitis externa. Note the dark, slimy and adherent discharge.

Figure 3: Cytology smear of the biofilm in Figure 2. Note the abundant, variably thick purple staining filaments forming a lace-like pattern (red arrow). There are numerous staphylococci (yellow arrow) and a single neutrophil (white arrow). Rapi-Diff stain, x 400.



Biofilms are clinically important as they inhibit cleaning, prevent penetration of antimicrobials and provide a protected reservoir of bacteria. Also, antimicrobials that require bacterial division will be less effective, as bacteria in biofilms are usually in a quiescent state. Biofilms may also enhance the development of antimicrobial resistance, especially in Gram-negative bacteria that acquire stepwise resistance mutations to concentration-dependent antimicrobials.

POTENTIAL IMPACT OF BIOFILMS ON ANTIMICROBIAL RESISTANCE

Biofilms generally inhibit antimicrobial penetration (see

Figure 4). Where this results in an abrupt drop in the antimicrobial concentration, most bacteria will either be exposed to high or low antimicrobial concentrations. Most will, therefore, be eliminated or unaffected. The unaffected bacteria in the biofilm will act as a reservoir and lead to treatment failure, but the selection pressure for resistance is relatively low. However, with some antimicrobial penetration into the biofilm and a gradual decrease in concentration, some bacteria will be exposed to intermediate concentrations. This could provide a mutant selection window in which the more susceptible bacteria are killed but more resistant mutants within the population survive. This will lead to treatment failure and recrudescence of the infection with a more resistant isolate.

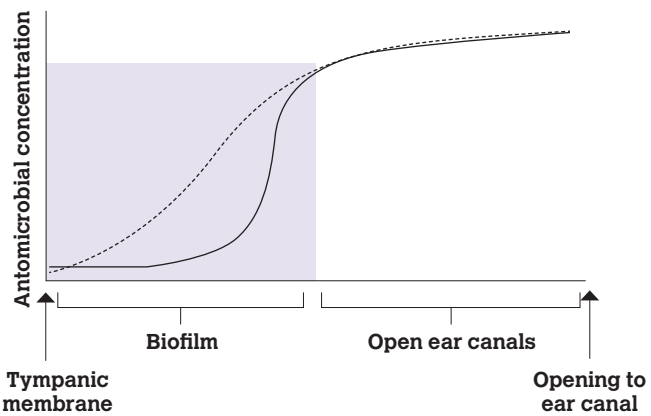


Figure 4: Potential impact of biofilms on bacterial resistance. There is an abrupt drop in concentration if the antimicrobial fails to penetrate the biofilm (solid line). The biofilm protects the bacteria leading to treatment failure, but there is relatively little selection for resistance. However, if the antimicrobial can partially penetrate the biofilm there may be a gradual drop in concentration (dotted line). The intermediate concentrations will kill more susceptible bacteria but allow more resistant mutants to survive and proliferate. This will result in treatment failure and recrudescence of the infection with a more resistant isolate. These data are taken from theoretical and in vitro studies.

BACTERIAL CULTURE AND SENSITIVITY TESTING

USING CYTOLOGY TO PREDICT SUSCEPTIBILITY PATTERNS

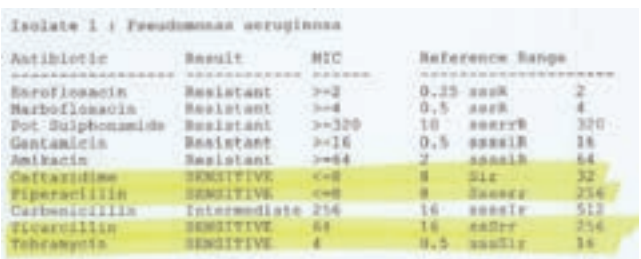
Bacterial culture and sensitivity testing is not necessary in most cases of otitis externa and/or where topical therapy is used. Cytology can effectively identify the most likely organisms in most cases of otitis. This is particularly useful in mixed infections, where culture may identify several organisms with different susceptibility patterns. *Malassezia* and staphylococci are easily identified and their likely sensitivity can be estimated from a knowledge of local resistance patterns and previous treatment. Gram-negative bacteria are harder to differentiate on cytology alone, although *Pseudomonas* are the most common. Their susceptibility pattern is harder to predict, although most first-time infections are susceptible to topical aminoglycosides, polymixin B, silver sulfadiazine and fluoroquinolones. However, *Pseudomonas* species readily acquire resistance and most isolates from recurrent infections will be multi-drug resistant.

USING BACTERIAL CULTURE AND ANTIMICROBIAL SENSITIVITY TESTING

Bacterial culture and sensitivity testing definitively identifies the bacteria involved in the infection. This can be useful for less common organisms that are hard to differentiate on cytology, eg. streptococci, enterococci, *Escherichia coli, Klebsiella*, *Proteus* and coryneforms. Knowledge of their likely sensitivity patterns can then help guide treatment choices.

UNDERSTANDING BREAKPOINTS AND RESISTANCE

The reported antimicrobial susceptibility results are less useful in otitis, especially with topical treatment. The breakpoints used to determine susceptibility or resistance assume systemic treatment. These are determined using pharmacokinetic data to estimate tissue levels following standard dosing. If the zone of inhibition around the antimicrobial disc representing the minimum inhibitory concentration (MIC) exceeds the breakpoint, it is unlikely that the antimicrobial will attain a therapeutic concentration in the target tissue and the infection can be regarded as resistant to that antimicrobial (see Figure 5). However, this does not necessarily mean that the bacteria are resistant to the antimicrobial, as sufficiently high levels may exceed the MIC.


Isolate 1 : Pseudomonas aeruginosa

Antibiotic	Result	MIC	Reference Range	
Enrofloxacin	Resistant	>=2	0.25 sssR	2
Marbofloxacin	Resistant	>=4	0.5 sssR	4
Pot Sulphonamide	Resistant	>=320	10 ssssrR	320
Gentamicin	Resistant	>=16	0.5 sssslR	16
Amikacin	Resistant	>=64	2 sssslR	64
Ceftaridime	SENSITIVE	<=8	8 Siz	32
Piperacillin	SENSITIVE	<=8	8 Sssssz	256
Carbenicillin	Intermediate	256	16 sssslr	512
Ticarcillin	SENSITIVE	64	16 ssSrr	256
Tobramycin	SENSITIVE	4	0.5 sssSiz	16

Figure 5: Antimicrobial susceptibility results for a multi-drug-resistant *Pseudomonas* isolated from a case of otitis externa in a dog. The results appear to indicate that there are only four suitable antimicrobials, but this is only true for systemic treatment. The row of letters in the reference range represent the range of antimicrobial dilutions that the isolate is cultured with (for enrofloxacin this is [right to left] 2.0µg/ml, 1.0µg/ml, 0.5µg/ml, 0.25µg/ml). The lower case letters refer to the accepted standards and the upper case letters refer to the actual MIC; in this case, the MIC for enrofloxacin is more than or equal to 2.0µg/ml (the highest tested concentration). The lower case 's' and 'r' ranges show the breakpoint following systemic dosing, 'i' refers to intermediate where the breakpoint is uncertain – in practice regard these as resistant. If the MIC falls within the 'r' range, then it is unlikely that the drug will attain a therapeutic concentration in the target tissue. Treatment is therefore unlikely to be successful and the infection should be regarded as resistant to that antimicrobial. If, however, the MIC falls within the 's' zone, then it is likely that the drug will exceed the therapeutic concentration in the target tissue. Treatment is likely to be successful, and the infection can be regarded as sensitive to that antimicrobial. Note that use of the term infection rather than bacteria; these results do not mean that an antimicrobial cannot eliminate the bacteria, only that systemic treatment would not be effective in that infection. The bacteria may still be eliminated by a sufficiently high concentration, which is why topical therapy is often effective even when *in vitro* test results show apparent resistance. This is particularly true for concentration-dependent antimicrobials (eg. aminoglycosides and fluoroquinolones), where the efficacy is proportional to the ratio between concentration and MIC. Sensitivity data is less useful for topical drugs because

concentrations in the ear canal are much higher than those used with *in vitro* tests predict. The response to treatment is best assessed using clinical criteria and cytology. Antimicrobial sensitivity data can be used to predict the efficacy of systemic drugs, although the concentration in the ear tissues is often low and high doses are needed. For example, enrofloxacin would need to be given at 20mg/kg to treat *Pseudomonas* isolates with an MIC of 0.5µg/ml (middle of the susceptible range in Figure 5 in chronic otitis.

TOPICAL AND SYSTEMIC ANTIMICROBIAL THERAPY

CHOOSING TOPICAL OR SYSTEMIC THERAPY

Topical therapy is preferred wherever possible. This results in high concentrations in the ear canals. Moreover, systemic antimicrobial therapy may be less effective in erythroceruminous otitis externa as organisms are present only in the external ear canal and cerumen, there is no inflammatory discharge and penetration to the lumen is poor.

Systemic treatment could be more useful in suppurative otitis externa and/or otitis media where there is an active inflammatory discharge with concurrent infection in the deep ear canal tissues and middle ear, although there is debate over this. Systemic treatment is more clearly indicated when the ear canal cannot be treated topically (eg, stenosis or compliance problems or if topical adverse reactions are suspected) and in otitis media.

TOPICAL ANTIMICROBIALS

Polymixin B, fusidic acid, florfenicol, gentamicin, enrofloxacin and marbofloxacin are suitable for most bacterial infections. Polymixin B and miconazole have synergistic activity against *Pseudomonas* and other Gram-negative organisms, and fusidic acid and framycetin show synergistic activity against staphylococci. Fluoroquinolones, gentamicin and polymixin B are usually effective against *Pseudomonas*. Fusidic acid and florfenicol are effective against meticillin-resistant *Staphylococcus aureus* and meticillin-resistant *Staphylococcus pseudintermedius* (Nuttall and Foster, 2015). Neomycin is less potent that other aminoglycosides, although it is usually effective against Gram-positive bacteria.

It is important to use an adequate volume to penetrate into the ear canals – 1ml is sufficient for most ears. The Easotic pump (Virbac) and Osurnia tubes (Elanco) accurately deliver 1ml doses, but it is difficult to achieve consistent dosing with other products. One solution is to draw the product up into a syringe for administration, ensuring that an appropriate dose is delivered each time.

The efficacy of concentration-dependant drugs (eg, fluoroquinolones and aminoglycosides) depends on delivering concentrations of at least 10 times the MIC once daily. Time-dependant drugs (penicillins and cephalosporins) require concentrations above the MIC for at least 70 % of the dosing interval. This is readily achieved with topical therapy, which achieves high local concentrations that probably persist in the absence of systemic metabolism. For example, concentrations of gentamicin have been shown to be three to 15 times and concentrations of miconazole 1.2 to 2.0 times the MIC90 for canine-otic isolates of staphylococci and *Malassezia*, respectively, 10 days after a five-day course of Easotic. Levels of florfenicol and terbinafine were at least 1,000 times the MIC90 for staphylococci and Malassezia, respectively, for the duration of treatment with two doses of Osurnia (Nuttall and Foster, 2015). Removal of debris and purulent material greatly improves the efficacy of topical antimicrobials, especially aminoglycosides and polymixin B. The antimicrobial activity of ear cleaners is variable, but has been shown to be associated with isopropyl alcohol, parachlorometaxylenol, chlorhexidine and a low pH. Acidic cleaners may inactive some antimicrobials (especially aminoglycosides and fluoroquinolones), although ear canals have good buffering capacity and the pH rapidly returns to normal.

SYSTEMIC ANTIMICROBIALS

Clindamycin, lincomycin, cefadroxil, cefalexin and clavulanate-potentiated amoxicillin are good first line drugs for *Staphylococcal* infections. Cefovecin is appropriate if compliance and/or administration are, or are likely to be, difficult. Fluoroquinolones are reserved for second line use where there is culture evidence that first-line drugs would not be appropriate. However, tissue penetration of antimicrobials with a low volume of distribution (eg. penicillins and cephalosporins) can be limited. Fluoroquinolones, which have a high volume of distribution and penetrate well into most tissues, may have better efficacy in infections otherwise susceptible to other antimicrobials. Itraconazole, ketoconazole and terbinafine (not licensed for use in animals) can be considered for *Malassezia* infections of both the external ear canal and middle ear, although *Malassezia* infections of the middle ear are rare.

PSEUDOMONAS OTITIS

Pseudomonas are resistant to many antimicrobials through low, cell-wall permeability,ß-lactamases, clavulanate-resistance and efflux pumps. They readily develop further resistance if treatment is ineffective as they have a large genome to express resistance genes and mutations, and are capable of plasmid, transposon and bacteriophage transfer. Once fluoroquinolone resistance is established other anti-*Pseudomonas* antimicrobials are indicated; these are often expensive, not licensed for animals and have to been given intravenously if used systemically (see Table 1).

* Not licensed for animals, these drugs and preparations should only be used where clinically justified under the Cascade and with the informed consent of the owners.

¶ Topical use in ears is not stated on the product label.

† Reconstituted solution stable for up to seven days at 4°C or one month if frozen.

Silver sulfadiazine shows additive activity with gentamicin and fluoroquinolones (although synergy has not been proven).

POTENTIAL TOXICITY OF ANTIMICROBIALS

Ticarcillin, polymyxin B, neomycin, tobramycin and amikacin are potentially ototoxic and should be used with care

if the tympanic membrane is ruptured. Neomycin and other components of topical products can cause contact

Antimicrobial	Delivery
Ciprofloxacin*	0.2% solution 0.15-0.3ml/ear q24h
Enrofloxacin¶	15-20mg/kg orally q24h; 2.5% injectable solution diluted 1:4 with saline or Epiotic (Virbac) topically q24h; 22.7mg/ml solution 1ml/ear q24h
Marbofloxacin¶	5-10mg/kg orally q24h; Aurizon (Vetoquinol) and Marbodex (Norbrook); 1% injectable solution diluted 1:4 with saline topically q24h; 20mg/ml solution 1ml/ear q24h
Ofloxacin*	Ofloxacin 0.3% 0.15-0.3ml/ear q24h
Carbenicillin*	10-20mg/kg intravenously q8h
Ceftazidime*†	25-50mg/kg intravenously q8h; 100mg/ml 1ml/ear q12-24h
Silver sulfadiazine*#	Dilute 0.1-0.5% in saline or trizEDTA; apply 1ml q24h
Polymixin B	Surolan (Elanco)
Amikacin*	10-15mg/kg subcutaneously q24h; 50mg/ml 1ml/ear q24h
Gentamicin	5-10mg/kg subcutaneously q24h; Otomax (MSD Animal Health) or Easotic (Virbac)
Tobramycin*	Use eye drops or 8 mg/ml injectable solution 0.15-0.3ml/ear q24h

Table 1: Antimicrobials that can be effective in *Pseudomonas* otitis.

reactions. Enrofloxacin, marbofloxacin, ceftazidime and silver sulfadiazine appear to be safe in the middle ear. There is potential for systemic toxicity with silver sulfadiazine and aminoglycosides in extensively ulcerated ears, although this is unlikely in practice as the total body dose will be low except in very small animals. The ototoxicity of gentamicin appears to depend on the preparation, and topical application of injectable solutions of gentamicin appears to be safe. Systemic aminoglycosides can be nephrotoxic and renal function should be monitored. Fluoroquinolones can cause cartilage damage in dogs under 12 months old (18 months in giant breeds), neurotoxicity at high doses, and blindness in cats (especially with injectable enrofloxacin).

TREATMENT OF BIOFILMS AND MUCUS

Biofilms can be physically broken up and removed by thorough flushing and aspiration. Topical trizEDTA and n-acetylcysteine can disrupt biofilms, facilitating their removal and enhancing penetration of antimicrobials. Systemic administration of n-acetylcysteine is well tolerated and can help dissolve biofilms in the middle ear and other mucous surfaces. Systemic n-acetylcysteine and bromhexine can also liquefy mucus, facilitating drainage in cases of primary secretory otitis media in dogs and feline inflammatory otitis media (polyps).

TRIZEDTA

TrizEDTA damages bacterial cell walls and increases antimicrobial efficacy, which can overcome partial resistance. It is best given 20 to 30 minutes before the antimicrobial but can be co-administered. It is well tolerated and non-ototoxic. TrizEDTA shows additive activity with chlorhexidine, gentamicin and fluoroquinolones at concentrations of 35.6/9.4mg/ml, but there is no evidence of synergy and efficacy at lower concentrations. Solutions of 0.6% enrofloxacin, 0.2% marbofloxacin, 0.3% gentamicin, 0.1% amikacin, 2.8% ticarcillin and 1.7% ceftazidime in trizEDTA are effective against many multi-drug-resistant bacteria including *Pseudomonas*.

EAR WICKS

Polyvinyl acetate ear wicks can be useful in certain cases. These are cut to size and inserted into the ear canal under anaesthesia, soaked with an antimicrobial, trizEDTA and/or steroid solution and left for three to 10 days, applying the ear solution once daily. The wicks absorb discharge and draw the antimicrobial solution into the ear canals. Steroid-soaked wicks can resolve stenosis of the ear and prevent stenosis following sharp or laser surgery to remove polyps and other masses within the ear canal. However, they may prevent drainage from the middle ear in cases of discharging otitis media and are contra-indicated in ears with copious exudates that need regular ear cleaning. Ear wicks are tolerated provided that they are kept moist.

TREATING OTITIS MEDIA

It is crucially important to flush out any debris from the middle ear cavity or pseudocavity formed from the invagination and extension of the tympanic membrane. This can only be done under general anaesthesia by passing a catheter into the middle ear. Otitis media may need three to four weeks (and possibly longer) systemic treatment, which is a problem if parenteral drugs are used. Pseudomonas infections, however, usually clear quickly once effective cleansing, antimicrobial treatment and control of the primary cause are established.
Opinion is divided on the systemic treatment of otitis media; some referral clinicians always use systemic treatment, others instil antimicrobials directly into the middle ear every three to 10 days (enrofloxacin, marbofloxacin, gentamicin, clotrimazole and miconazole appear to be safe used in this way), some use topical therapy and some a combination of approaches. It is likely that antimicrobials persist for several days following direct application into the middle ear, because this is effectively a blind-ending sac with limited drainage into the pharynx.

ANTI-INFLAMMATORY TREATMENT

Reducing pruritus, swelling, exudation and tissue proliferation is a key goal of therapy, and maintenance treatment is necessary in ongoing conditions such as atopic dermatitis (see Figure 6). Glucocorticoids (particularly dexamethasone) also reverse the ototoxic effect of *Pseudomonas* infections.

USING TOPICAL OR SYSTEMIC GLUCOCORTICOIDS

The choice largely depends on the severity of the otitis. It is important to carefully assess the degree of pain, firmness, mobility, erythema, swelling, fibrosis and stenosis of the ear canals by palpation and otoscopy.

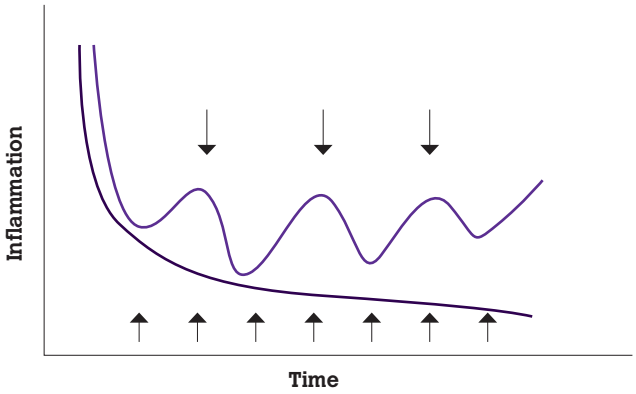


Figure 6: Successful long-term management of otitis secondary to chronic inflammatory conditions, such as atopic dermatitis, requires ongoing regular anti-inflammatory treatment to maintain remission and prevent relapses of infection. Such proactive therapy (the lower orange line) gives a much better prognosis. Reactive treatment of each bout of infection (the upper red line) gives short-term relief, but misses the ongoing inflammation in the absence of infection. This allows chronic inflammatory changes to develop that will result in more frequent and severe infections. These cases will eventually need a total ear canal ablation

Topical therapy is preferred as this delivers the drug to the affected site avoiding systemic exposure, and most polyvalent ear products contain a glucocorticoid. Systemic treatment is necessary if there is stenosis, severe fibrosis or mineralisation, or if topical therapy cannot be safely administered. It is usually possible to switch to topical therapy once the ear canals have opened. Animals better tolerate topical therapy once the pain has decreased.

Potency	Glucocorticoid
Very potent glucocorticoids (up to 100 x hydrocortisone)	Fluocinolone
Potent glucocorticoids (25-100 x hydrocortisone)	Betamethasone Dexamethasone Hydrocortisone aceponate Mometasone furoate
Moderate glucocorticoids (2-25 x hydrocortisone)	Prednisolone Triamcinolone
Mild glucocorticoids	Hydrocortisone

Table 2: Relative potency of topical glucocorticoids. Table 2 should be used for guidance only, as the relative potency of topical glucocorticoids also varies with the concentration, formulation and preparation. Topical therapy is safer than systemic therapy but adverse effects can be seen, for example, the hypothalamic-pituitary-adrenal (HPA) axis can be affected for up to two to four weeks after otic administration of dexamethasone. Hydrocortisone aceponate and mometasone furoate show less local atrophy and systemic absorption than other glucocorticoids. Atrophic effects can be useful in reversing fibrosis and stenosis early in treatment, but may later interfere with epidermal migration allowing debris and desquamated cells to accumulate in the ear canals.

TOPICAL GLUCOCORTICOIDS

The glucocorticoids incorporated in topical ear medications are appropriate for managing mild to moderate inflammation in acute otitis externa. Use of antimicrobial-containing products, however, is not indicated in the absence of infection.

There is a variety of glucocorticoid-containing eye drops, ear drops and ear cleaners available, although these may not be licensed for use in animals. Soluble glucocorticoid preparations can also be added to trizEDTA solutions to create rinses with an appropriate glucocorticoid concentration (eg. 0.1% dexamethasone [again, not licensed for use in animals). Mild inflammation responds rapidly to low-potency topical glucocorticoids, but progressively more severe inflammation requires longer courses of more potent products (see Table 2). Very potent products should be avoided in severe bacterial infections, particularly *Pseudomonas*, as they may suppress neutrophil activity. Once the otitis has resolved, topical glucocorticoids should be used at the lowest frequency that controls the inflammation.

SYSTEMIC GLUCOCORTICOIDS AND OTHER ANTI-INFLAMMATORY AGENTS

Prednisolone (1 to 2mg/kg every 12 to 24 hours) or methylprednisolone for one to three weeks is sufficient to control inflammation and stenosis in most cases. Patients with severe fibrosis and stenosis, however, may respond better to betamethasone or dexamethasone (7.5 to 10 times as potent as prednisolone). Ciclosporin has also been shown to be effective in some cases of chronic otitis. Long-term treatment usually involves prednisolone, methyl-prednisolone or ciclosporin used at the lowest frequency and dose that prevents recurrence of the otitis (particularly as this helps to manage underlying allergic conditions that give rise to the otitis). Dexamethasone can be used with care twice weekly.

COMPLIANCE AND ADHERENCE

Poor compliance or adherence will compromise efficacy and encourage resistance. Compliance problems include under-dosing, missed doses and stopping treatment early. Discussing potential problems openly and honestly with owners helps to select the most appropriate drug and dosing regime. Compliance can be improved by:

- Using long duration topical or injectable, once daily and/or palatable medication;
- Using drugs that the owner is able to and wants to administer;
- Convincing the owner of the importance of correct treatment;
- Giving written instructions;
- Demonstrating how to administer topical therapy and how to clean ears;
- Using precise terminology, eg. 'every 12 hours' instead of 'twice daily';
- Good follow-up and communication;
- Minimising the number of different drugs or treatments;
- Using analgesia to facilitate cleaning and topical medication;
- Recommending regular revisits to assess the ear disease; and
- Emphasising that management and control is the aim, not usually cure of chronic otitis.

REFERENCES ON REQUEST