Selecting ear drops for dogs with otitis externa

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Otitis externa is one of the most common conditions presenting in canine practice. Ear disease often reflects a combination of predisposing, primary, perpetuating and secondary factors. While the animal health industry has provided veterinary surgeons with a wide array of safe, effective and licensed topical products, simply dispensing ear drops will not satisfactorily resolve otitis externa in a significant proportion of cases. Veterinary use of antimicrobial drugs is currently under intense scrutiny, prompting the BVA to produce an eight-point plan on responsible use. This article discusses the use of antimicrobial products in canine otitis externa in relation to these guidelines, with emphasis on rational product selection and minimising antimicrobial use where appropriate.

Otitis externa is one of the most common presentations in canine practice. In a survey of 3707 small animal consultations observed by veterinary students during clinical extramural studies (EMS) in general practice in the UK, otitis externa was diagnosed in 123 out of 559 dogs (22 per cent) with skin disease (Hill and others 2006). Eighty-eight of these received antibiotic-containing ear drops, although the proportion that received systemic therapy for otitis was not reported. Discussions with final year veterinary students about their experiences during EMS indicate that the rationale for selecting one otic product over another is often not clear to them (and perhaps not to the attending veterinary surgeon either). The survey by Hill and others (2006) indicates that product selection in skin disease is routinely empirical; out of 795 small animal dermatological consultations (including 151 cases of otitis), otoscopic examination was conducted in 90 cases, cytology in 31 of 795 cases, and bacterial culture and sensitivity in just eight cases.

The increasing emergence and heightened awareness of antimicrobial resistance in human and animal health has prompted the British Veterinary Association (BVA), British Small Animal Veterinary Association and Veterinary Medicines Directorate each to produce their own guidelines and information on responsible antimicrobial use in veterinary practice. The present review considers otic product selection in relation to the points proposed in the BVA's eight-point plan, where relevant to the topical treatment of otitis externa.

Work with clients to avoid the need for antimicrobials

Microbial infection within the canine external ear canal often reflects proliferation of normal components of the skin microbiota (commonly *Staphylococcus pseudintermedius* or *Malassezia pachydermatis*) or invasion by environmental opportunistic Gram-negative bacteria such as *Pseudomonas aeruginosa*. Since ear infection is considered to be a 'secondary factor' in otitis externa that reflects the

Table 1: Preventative and therapeutic strategies for predisposing factors in canine otitis externa

Predisposing factor	Control strategy
Conformation – stenotic ears	Anatomical: consider lateral wall resection (Inflammatory: use anti-inflammatory drugs while correcting aetiology)
– hair in ear canals/pinnae	Regular removal?
– pendulous pinnae	Nil other than breeding
Excessive moisture	Limit swimming in susceptible dogs
	Limit/balance application of treatments
Treatment effects	Avoid irritant topical agents and trauma from cotton applicators
Neoplasms/polyps	Early diagnosis and treatment
Systemic disease (pyrexia, immunosuppression)	Early diagnosis and treatment

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presence of 'predisposing', 'primary' and 'perpetuating factors', prevention and control of these other factors will reduce the frequency of ear infection and the need for antimicrobial drugs (Tables 1 and 2). Clients should be routinely encouraged to cooperate in a proper investigation of the factors favouring otitis externa in their pets so that the need for repeated prescriptions of antimicrobial drugs can be avoided (Fig 1).

Avoid inappropriate use

The BVA guidelines state that use of antimicrobial drugs should be restricted to affected or at risk animals, and that clients should be instructed on proper administration for the full course without underdosing. Antimicrobials are clearly indicated in the presence of infection within the ear canal, but not all animals with otitis externa have active microbial infection. For example, some dogs with primary allergic disease have inflamed ear canals without microbial overgrowth, although opportunistic infection is certainly common in allergic dogs. Some dogs with previous otitis externa subsequently re-present with mildly inflamed ear canals containing a light-coloured discharge, representing sloughed epithelial cells from maceration induced by over-use of ear cleaner; treatment should consist of product withdrawal rather than antimicrobial therapy.

Cytology

The key step in determining the need for antimicrobial therapy is ear cytology. Hill and others' survey indicates that few practitioners routinely adopt this simple, inexpensive and informative procedure, whereas specialists consider this fundamental to the management of every case. The general rule is to 'treat what you see'; microbial populations, where present, may be represented by yeasts and/or coccoid bacteria and/or rod-shaped bacteria (Fig 2). Cytology is also especially useful for monitoring the efficacy of antimicrobial treatment and changes in the nature of the microbial infection, for example, a switch from bacterial to *Malassezia* species infection.

Fig 1: Erythemato-ceruminous otitis externa with *Malassezia* otitis as a secondary factor is accompanied by erythema of the pinna, reflecting atopic dermatitis, the underlying primary disease in this case

Table 2: Preventative and therapeutic strategies for primary factors in canine otitis externa

Primary factor	Control strategy
Parasites	Acaricidal ear drops or spot-on endectocides
Hypersensitivity diseases (atopic dermatitis, food, contact, drug)	Allergen avoidance where practicable, or anti-inflammatory drugs, or allergen-specific immunotherapy (atopic dermatitis)
Keratinisation disorders (idiopathic seborrhoea, endocrinopathies)	Early diagnosis and specific treatment
Foreign bodies	Prompt removal; modify exercise location if grass seed present
Autoimmune diseases	Early diagnosis and specific treatment

Method of treatment

A serious practical limitation to the successful management of ear cases can be the method and frequency of application of ear treatments. Careful owner instruction on techniques for application is time well spent. Owners should be shown how to restrain their pet and apply the treatments. Many companies provide literature for owners explaining the treatment process in detail. Ear cleaners can be administered using syringes so that accurate and defined volumes can be applied; having one for each ear prevents any cross-contamination of microbial pathogens. Alternatively, single-use vials are also available.

Choose 'the right drug for the right bug'

The BVA suggests that target organisms should be identified, their susceptibility predicted, and treatment initiated using antimicrobials with as narrow a spectrum as possible. Cytological evaluations enable the clinician to establish the general nature of any microbial pathogen quickly and inexpensively, although culture is often needed for specific identification. Cytology and culture can yield discordant results (Graham-Mize and Rosser 2004), and care is needed to ensure that swab samples are representative; for example, some dogs have wax with few organisms in the vertical canal but purulent exudation and bacterial infection in the horizontal canal.

Antifungal drugs

The monopolar budding of *Malassezia* species results in a distinctive peanut-shaped morphology readily recognised in cytological preparations. All six of the licensed antimicrobial ear drop products available in the UK contain an antifungal drug (Table 3) and claim efficacy in treating fungal otitis externa, but comparative clinical trial data are limited (Bond and others 2010). *Malassezia* species are normally susceptible to azoles (such as clotrimazole and miconazole) and polyene macrolides (such as nystatin). The very high in vitro activity of the recently developed triazole, posaconazole, against *M pachydermatis* is reflected by the low final concentration in the product (Table 3).

Antibiotics

Coccoid bacteria from infected ear canals of dogs often represent staphylococci, streptococci or

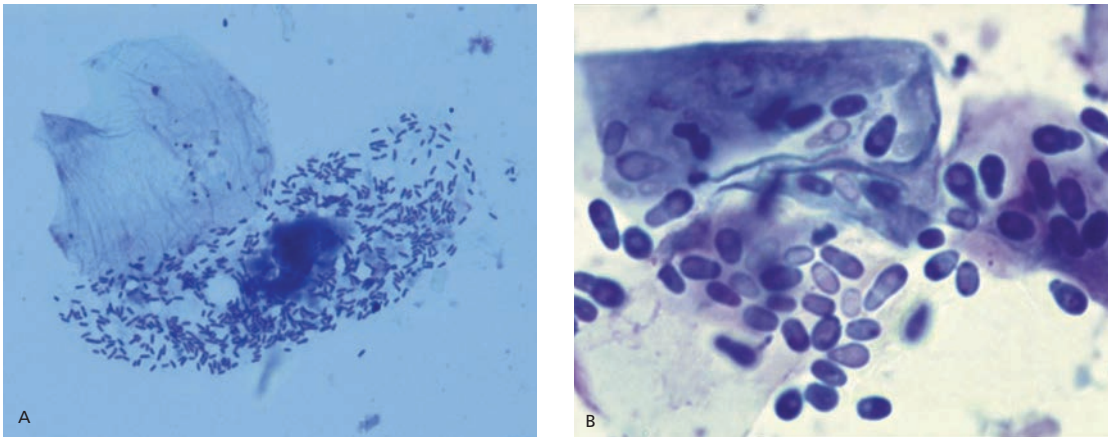

Fig 2: (a) Cytological smear from the horizontal canal of a dog with *Pseudomonas aeruginosa* otitis externa and media; large numbers of rods are apparent among squames. (b) Numerous peanut-shaped yeasts with the characteristic morphology of *Malassezia* species from the external ear canal of a dog

enterococci, whereas rods are often examples of pseudomonads or coliforms. In most studies, *S pseudintermedius* is the most common bacterial pathogen, being isolated from 45 to 60 per cent of cases; streptococci and enterococci may be isolated from up to 30 per cent of cases, and *Pseudomonas aeruginosa* from up to 18 per cent of cases, although isolation rates of pseudomonads may reach 26 per cent in chronic cases seen in referral centres (Cole and others 1998, Graham-Mize and Rosser 2004, Hariharan and others 2006, Lyskova and others 2007). Antibiotic resistance can be of particular concern among the Gram-negative rods, although multidrug-resistant staphylococci are an increasing threat in canine practice (Fig 3).

Although the guidelines recommend that narrow-spectrum antibiotics are utilised wherever possible, topical ear drop products contain broad-spectrum agents, reflecting both the wide array of different bacterial genera that infect dogs' ears and the not infrequent tendency to mixed infection. Antibiotic groups represented in licensed products include steroidal antibiotics (fusidic acid), cationic polypeptides (polymyxin B sulphate), aminoglycosides (neomycin, framycetin [neomycin B], gentamicin), and fluoroquinolones (marbofloxacin, orbifloxacin).

- Fusidic acid is generally active against only Gram-positive bacteria and therefore it is formulated with an aminoglycoside (framycetin) to extend that product's spectrum to Gram-negative pathogens.
- Aminoglycosides are particularly valuable for treating Gram-negative infections but many streptococci and enterococci are inherently resistant, at least at concentrations achieved by systemic administration (Graham-Mize and Rosser 2004, Moyaert and others 2006).
- Polymyxins are generally active against Gram-negative rods (*P aeruginosa* and to a lesser extent, staphylococci and streptococci) (Pietschmann and others 2009), whereas *Proteus* species are naturally resistant to polymyxins (Rozalski and others 1997). Synergistic interactions between polymyxin and miconazole have been reported against *Escherichia coli* and *P aeruginosa* (Pietschmann and others 2009).
- The fluoroquinolones have a broad spectrum of activity against many Gram-positive and Gram-negative bacterial pathogens of the ear canal. BVA guidelines (and the products' datasheets) indicate that fluoroquinolones should be reserved for clinical conditions that respond poorly to other classes of antimicrobials and where antibiotic sensitivity testing has been carried out (see later).

Glucocorticoid potency

Six different glucocorticoids of varying potency and concentration are represented in the six steroid-containing products (Table 3); typically the more potent steroids are present in lower concentrations. Glucocorticoids are often beneficial because control-

Table 3: Composition of antimicrobial ear drop products licensed for use in canine otitis externa in the UK (in alphabetical order of trade name)

Product	Antifungal agent	Antibacterial agent(s)	Glucocorticoid
Aurizon	Clotrimazole 10 mg/ml	Marbofloxacin 3 mg/ml	Dexamethasone 0.9 mg/ml
Canaural	Nystatin 100,000 iu/g	Diethanolamine fusidate 5 mg/g Framycetin 5 mg/g	Prednisolone 2.5 mg/g
Easotic	Miconazole 15.1 mg/ml	Gentamicin 1505 iu/ml	Hydrocortisone aceponate 1.11 mg/ml
Otomax	Clotrimazole 8.8 mg/ml	Gentamicin 2640 iu/ml	Betamethasone 0.88 mg/ml
Posatex	Posaconazole 0.9 mg/ml	Orbifloxacin 8.5 mg/ml	Mometasone furoate 0.9 mg/ml
Surolan	Miconazole 23 mg/ml	Polymyxin B 0.53 mg/ml	Prednisolone 5 mg/ml

ling underlying primary inflammatory diseases often reduces the susceptibility to infection, and their use can prevent or correct progressive changes such as hyperplasia and stenosis. A discussion of the relative merits of the different steroids is beyond the scope of this article.

Product selection

It could be argued that since all the products listed are antibacterial and antifungal, any one of them could be considered a reasonable choice for treating canine otitis externa. On the other hand, recognising the target pathogens by cytology or culture can aid in product selection. From the BVA guidelines, it is difficult to justify use of a product containing a fluoroquinolone in first line, uncomplicated cases of yeast or coccoid bacterial infection. Fusidic acid is often a logical choice for coccoid bacterial infections. Both nystatin-containing (Canaural; Dechra Veterinary Products) and miconazole-containing (Surolan; Elanco Animal Health) products eliminated *Malassezia* species from the ear canals of a group of 60 foxhounds with otitis externa when applied for five days out of eight (McKellar and others 1990). These two products are attractive for uncomplicated *Malassezia* otitis cases where a highly potent antibiotic (such as gentamicin or a fluoroquinolone) is not needed. By contrast, gentamicin and fluoroquinolone-containing products are frequently indicated in cases of otitis associated with Gram-negative infections, especially if there is a lack of response to the less potent aminoglycosides (framycetin, neomycin) or polymyxin. The gentamicin- and fluoroquinolone-containing products all contain potent azole antifungal agents likely to be effective in mixed infections with yeast and Gram-negative bacterial infections.

Monitor antimicrobial sensitivity

The BVA guidelines recognise that initial treatment is often based initially on clinical diagnosis but state that sensitivity must be determined wherever possible so that a change in treatment can be implemented if necessary. However, there are some important limitations in microbial culture and sensitivity testing in canine otitis externa.

Many diagnostic microbiology laboratories routinely undertake disc sensitivity testing, wherein the zone of growth inhibition around the antibiotic disc is related to the minimum inhibitory concentration for the pathogen. In addition to many technical variables associated with these methods that can influence the results, the breakpoints used to determine sensitivity and resistance for some antibiotics are optimised for antibiotic concentrations achieved following systemic administration, often in humans. The concentrations achieved by correct topical application in the ear will be substantially higher than those obtained by oral use, and therefore bacteria reported as 'resistant' might still be successfully killed. Some laboratories report sensitivity data for *M pachydermatis* but standardised laboratory methods for this species are not yet established (Velegraki 2010), and there are, to date, only rare reports of azole-resistant *M pachydermatis* (Nijima and others 2011).

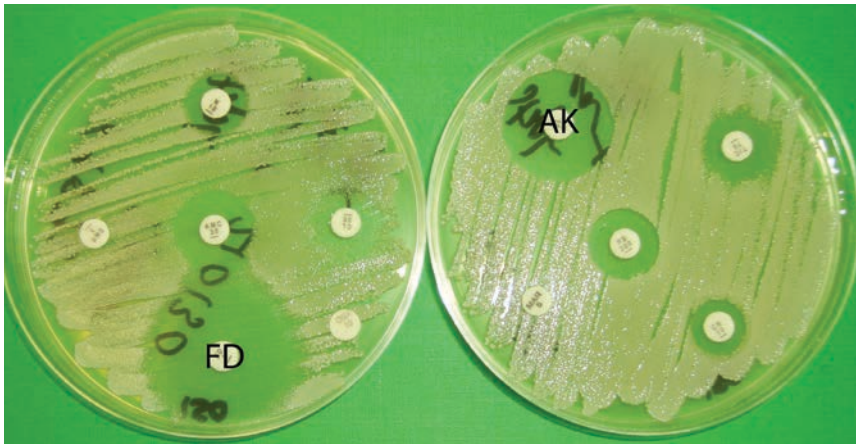

Fig 3: Disc sensitivity testing of a strain of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) isolated from the tympanic bulla of a dog during a total ear canal ablation/lateral bulla osteotomy. Like many examples of European MRSP, this isolate was sensitive to fusidic acid and amikacin but resistant to beta-lactam and fluoroquinolone antibiotics

Minimise prophylactic use of antimicrobials

Prophylactic use of antimicrobials in canine otitis externa can be minimised by systematic attempts to investigate and treat the predisposing and primary factors favouring otitis externa outlined in Tables 1 and 2. In circumstances where the tendency for otitis remains or where the normal self-cleaning mechanism of the ear is deficient, ear cleaners may prove useful, since a number of these products have components with antimicrobial activities. The use of ear cleaners for prophylaxis needs to be balanced with the risk of maceration or irritation from regular application.

Controversies and difficulties in treating otitis

There are few high-quality comparative clinical trial data available on the relative merits of different products. Such trials are difficult to design, perform and standardise, given the complex aetiology inherent in cases of otitis externa. Product selection in this area is likely influenced by subjectivity, prescribing habit, and commercial aspects of product supply. However, a wider uptake of ear cytology and culture in general practice would, in the author's view, lead to more targeted antimicrobial therapy and better case outcomes.

Duration of treatment

Adequate duration of antimicrobial treatment is important for clinical efficacy and to limit resistance. The current EU regulatory framework appears to be driving short (five- to seven-day) licensing for new otic products for dogs, whereas the clinicians in the author's group routinely prescribe ear drops for longer than one week. Although these clinicians operate in a referral environment, seven days may

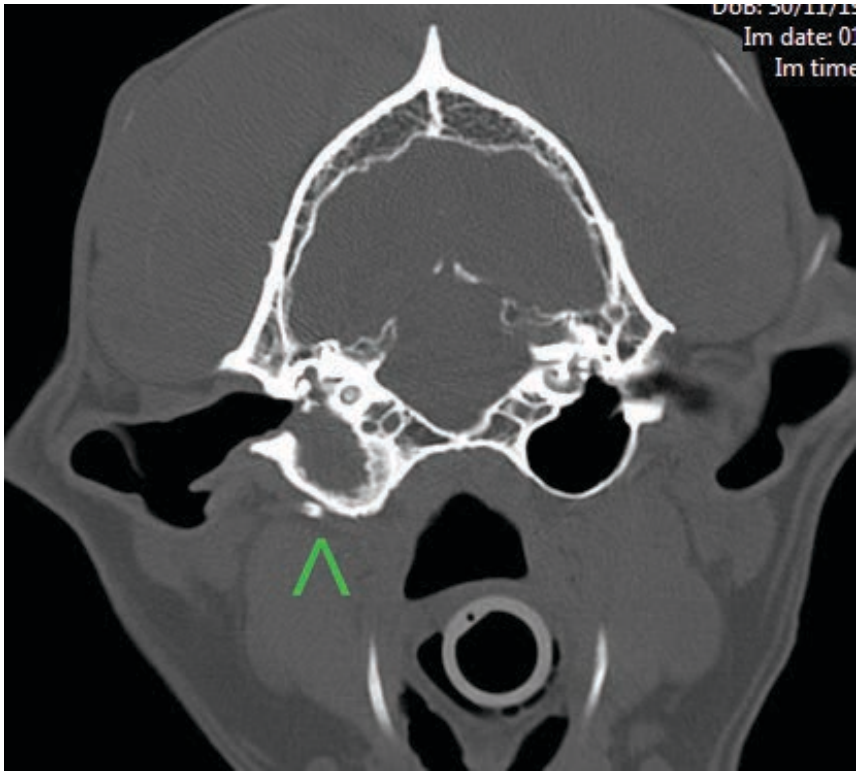

Fig 4: Computed tomography scan of a dog with unilateral otitis media; there is a soft tissue opacity filling the tympanic bulla along with bone thickening (green arrowhead)

not be sufficient for many cases in first-opinion practice either. In a randomised, blinded, multicentre study that compared the efficacy of a combination of marbofloxacin-clotrimazole-dexamethasone with a polymyxin B-miconazole-prednisolone product for the treatment of acute or sub-acute otitis externa of less than 30 days' duration, 15 dogs (eight with the former product, seven with the latter) were satisfactorily treated with a seven-day course, whereas 55 dogs (34 with the former product, 21 with the latter) required treatment for 14 days (Rougier and others 2005). Chronic cases may require even more prolonged treatment. The duration of treatment should be sufficient to ensure clinical and microbiological resolution of otitis externa.

Yeast infections

It is ironic that the prescribing cascade dictates the use of antibiotic-containing ear drop products in cases of yeast infection. Many dermatology specialists would like to have an antifungal-steroid combination without an antibiotic available for the treatment of uncomplicated canine *Malassezia* otitis externa. Although there is a risk that yeast removal might permit bacterial proliferation within the ear, many azoles have activity against coccoid bacteria as well. Clearly such a product would have the advantage of limiting unnecessary antibiotic usage in cases of yeast infections. However, unless and until cytological assessments become routine in veterinary practice, it is difficult to imagine such a product gaining wide acceptance, since its efficacy in cases of bacterial infection, especially with Gram-negative pathogens, would be poor. It is most important that products combining antibacterial and antifungal agents are available for cases with mixed infection, and in circumstances where cytological assessments are not performed.

Otitis media

Progression to otitis media is not uncommon in cases of canine otitis externa (Fig 4). To the author's knowledge, there are no veterinary medicinal products licensed for use in the canine middle ear. The existing products' datasheets specify that these products should not be used when the tympanic membrane is ruptured, but that cannot always be readily established, especially on first presentation. Veterinary surgeons are routinely in the invidious position of having to use potentially ototoxic drugs in circumstances where the status of the tympanic membrane is either unknown or known to be ruptured. Informed owner consent should be carefully documented in these circumstances.

Cleaning the ear

There is general consensus that cleaning the ear is an essential part of the management of ceruminous or purulent otitis externa. Purulent exudate presents a hyperosmolar, hypoxic and acidic environment that impairs the efficacy of many antimicrobials, such as polymyxin B and gentamicin (Bryant and Hammond 1974). Several different cleaning products are available, but compatibility with the antimicrobial products is largely unknown and studies are urgently required.

Summary

The veterinary profession is fortunate that the animal health industry has provided it with both well-proven products and products with newer chemistries for the treatment of otitis externa. Our profession must be able to show responsible use of antimicrobial drugs if restrictions on availability from regulators are to be avoided in the future.

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Self assessment test: Selecting ear drops for dogs with otitis externa

1. Match the following antibacterial components with the commercial formulation.

(a) Diethanolamine fusidate	(i) Posatex
(b) Marbofloxacin	(ii) Easotic/ Otomax
(c) Orbifloxacin	(iii) Surolan
(d) Polymyxin B sulphate	(iv) Canaural
(e) Gentamicin	(v) Aurizon

2. Match the following antifungal or steroidal components with the commercial formulation.

(a) Clotrimazole	(i) Posatex
(b) Posaconazole	(ii) Otomax
(c) Mometasone furoate	(iii) Easotic
(d) Hydrocortisone aceponate	(iv) Canaural
(e) Nystatin	(v) Aurizon

Answers

1. a, iv; b, v; c, i; d, iii; e, ii

2. a, ii and v; b, i; c, i; d, iii; e, iv

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