Managing recurrent otitis externa in dogs – what have we learned and what can we do better?

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Abstract

Recurrent otitis externa is a common problem in dogs. Topical treatment for each flare is successful in the short term but repeated cycles of inflammation and infection lead to chronic inflammatory changes, pain and aversion, and antimicrobial resistance. These make the flares more frequent and harder to control. Eventually, the changes become irreversible and require a TECA/LBO or ablative laser surgery. Most ear canal surgery is avoidable if recurrent otitis is properly managed at an earlier stage. This requires a different mindset and approach to these cases, taking advantage of recent research and clinical findings. Most importantly, clinicians must appreciate that all recurrent ear infections in dogs are secondary. To achieve a good long-term outcome, it is essential that all the underlying factors in each case are diagnosed and managed using the Primary, Secondary, Predisposing and Perpetuating (PSPP) framework. This means that the primary condition must be diagnosed and managed, the secondary infection treated, predisposing risks identified and corrected, and the perpetuating factors reversed. Treatment is in two phases: induction to get the ears in remission, and then long-term maintenance therapy to prevent relapses. Treatment should be appropriate to each dog, but will typically involve ear cleaning, topical antimicrobial therapy, and topical or systemic glucocorticoids. Novel treatments for infection and inflammation will offer additional options in the future. Understanding the triggers for recurrent otitis in dogs will help clinicians plan effective management regimens that will make a huge difference to the quality of life of their patients and their owners.

Introduction

Otitis externa is common in dogs[1]. Recurrent cycles of inflammation and infection lead to chronic acquired pathological changes that make the flares of infection more frequent and severe. These changes may also drive a switch from *Malassezia* yeasts and/or Gram-positive bacteria to Gram-negative bacteria, particularly *Pseudomonas* spp. *Malassezia* and bacterial species associated with otitis produce biofilms, which facilitate adherence, promote complex and self-sustaining microbial populations, and inhibit antimicrobial activity[2,3]. Finally, repeated ineffective treatment courses select for antimicrobial resistance (AMR)[4]. Eventually, there are irreversible changes and/or unresponsive infections that require surgical intervention, most commonly total ear canal ablation/lateral bulla osteotomy (TECA/LBO). This may be curative in terms of removing the diseased tissue but substantially increases the cost and complexity of treatment (which can include haemorrhage, pain, surgical site infections, Horner's and/or vestibular syndrome, and para-aural abscesses). Most ear canal surgery is avoidable if recurrent otitis is correctly diagnosed and managed to prevent the march to irreversible chronic changes. However, this necessitates a thorough understanding of the aetiology and pathogenesis of otitis. This review will discuss modern approaches to recurrent otitis in the light of new evidence around inflammatory diseases and the otic microbiome. It will concentrate on otitis externa and only briefly discuss otitis media and interna.

Definitions

There are no agreed definitions for recurrent and chronic otitis. In our practice, we use:

- *Otitis* – inflammation of the pinnae and/or ear canals; this may or may not be associated with infection.

- *Ear infection* – a clinically significant microbial overgrowth or infection, although in most cases this represents a dysbiosis of the local otic microbiome rather than a true acquired infection (see below).
- *Recurrent* – clinically significant ear inflammation/infection within 3 months of complete resolution of a previous episode; this may be acute or chronic.
- *Acute* – otitis without acquired proliferative changes in the ear canals (figure 1).
- *Chronic* – otitis with the presence of acquired proliferative changes in the ear canals (figure 2).

There are two distinct clinical presentations of otitis externa

Most cases of otitis fall into one of two distinct clinical presentations:

- *Erythroceruminous otitis* – characterised by erythema with a ceruminous to seborrhoeic discharge (figure 3). The ears may simply be inflamed, but most cases are associated with *Malassezia* yeasts or staphylococcal bacterial overgrowths; Gram-negative bacteria are less common unless there is chronic inflammation and stenosis. These cases tend to pruritic, but chronically inflamed ears can be painful.
- *Suppurative otitis* – characterised by erythema, ulceration and a purulent discharge often with a biofilm (figure 4). Most cases are associated with neutrophils and *Pseudomonas* spp. with other Gram-negative and Gram-positive bacteria less common. *Malassezia* yeasts are rare in suppurative otitis[5] but show a distinct phenotype that may be associated with IgE-associated *Malassezia* hypersensitivity and immune-mediated ear canal inflammation (including interface dermatitis). Non-infected suppurative otitis is less common but can be seen with irritant reactions to topical treatments or immune-mediated diseases that affect the ear canal[6]. Suppurative otitis is often very painful.

All recurrent ear infections are secondary

All recurrent ear infections are secondary to underlying factors[7,8]. It is important to note that while published 'cure' rates for topical antimicrobial/glucocorticoid ear medications are very high (often over 90%), these refer to the individual episode of *ear infection* and not the underlying *otitis*. Recurrence does not mean that the treatment failed, but it does mean that the underlying triggers for the otitis and ear infections were not managed. Repeating treatment with the same or a different product will only give short term relief - this will not alter the pattern of relapsing inflammation and infection. It is essential that the underlying triggers are diagnosed and managed for a successful long-term outcome.

There are primary, predisposing and perpetuating triggers for otitis externa

The development and progression of recurrent and/or chronic otitis is multifactorial. The primary-predisposing-perpetuating (PPP) system is a well-established framework to identify the primary, predisposing and perpetuating factors in each case[9]. More recently, this has been modified to a PSPP/PPPS system to include the secondary (S) infections[10] (see above).

Primary triggers in otitis externa

Primary factors trigger the ear inflammation and, therefore, must be capable of inducing inflammation in otherwise healthy skin or, less commonly, suppress the immune system to the extent that potential pathogens can establish in the ear canals factors[7-9] (table 1).

There is a wide range of potential primary triggers of otitis externa but it makes no sense to investigate all of these in every case. A careful and thorough review of the signalment, history and clinical signs (making sure that the whole dog is examined, not just the ears) will narrow the differential diagnosis allowing cost- and time-efficient use of appropriate

diagnostic steps and treatment. For example, a three-year-old Labrador retriever with a history of recurrent bilateral erythroceruminous otitis with pruritus and erythema of its ventral pinnae, interdigital skin and flexor joint surfaces is highly likely to have atopic dermatitis and/or an adverse food reaction. A cocker spaniel with acute and painful unilateral otitis after exercising in long grass is most likely to have a grass awn lodged in the ear canal.

It is very important to take a holistic view of each case – clinicians must recognise and understand the clinical significance of findings that help identify the underlying condition or at least narrow the options. It is crucial to fully examine both ears even in cases of apparent unilateral otitis. Bilateral otitis is more common but local predisposing factors (see below) can make the otitis more common or more severe in one ear than the other. The subsequent chronic acquired perpetuating changes (see below) lead to further divergence in severity between the two ears. In our practice, most referrals with unilateral otitis actually have bilateral disease. This changes the most likely differentials as well as the approach to investigation and treatment. While some cases of atopic dermatitis may present with unilateral otitis it is important to consider other triggers in these cases.

Predisposing factors in otitis externa

Predisposing factors rarely (if ever) trigger otitis by themselves but they make the otitis more likely to occur or more likely to progress in an animal with a primary condition[9] (table 2). These are mostly anatomical/conformational or (less commonly) lifestyle or management factors[1].

Cocker spaniels, especially American cocker spaniels, have a greater density of ceruminous glands than other breeds[11,12]. This predisposes them to ceruminous gland hyperplasia,

ectasia and cyst formation that results in rapid development of chronic changes (i.e. perpetuating factors - see below). These changes facilitate bacterial infections and are less responsive to glucocorticoid therapy, which may be why these breeds rapidly progress to end-stage otitis requiring TECA-LBO[11,12] (figure 5).

Chinese shar pei have a tightly opposed rostrally facing pinna that is partly the outcome of a twist in the vertical ear canal. In some dogs, this results in stenosis at that point. Prophylactic vertical ear canal surgery may be of benefit in these dogs. However, this must be done before chronic inflammatory changes develop in the horizontal ear canal.

Perpetuating changes in otitis externa

Perpetuating changes are chronic acquired pathological changes in the ear canals that prevent resolution[9]. Early changes include nodular epidermal and glandular hyperplasia giving the ear canals a 'cobblestone' appearance (figure 2). Later changes include further epidermal and dermal hyperplasia and thickening, ear canal stenosis and occlusion, fibrosis and mineralisation. This can also result in tympanic membrane rupture, otitis media and cholesteatoma formation.

It is essential that early chronic acquired pathological changes are recognised and treated. This gives the best chance of a good long-term outcome. More severe changes become progressively harder to treat increasing the complexity, complications and cost.

Assessing the extent and severity of chronic pathological changes in otitis externa

Acquired perpetuating changes must be reversed during the initial induction phase of treatment (see below). Treatment planning therefore needs a thorough assessment of their

extent and severity. Traditionally, this has relied on diagnostic imaging but clinicians should also use their clinical acumen (especially if finances or resources are limited).

Healthy ear canals are thin cartilage tubes lined by skin – they should be freely mobile, pliable, and free from discharge, pruritus and pain. Affected ear canals will become progressively immobile, firm and painful. Otoscopic examination should reveal a thin, smooth and pale lining with scant ceruminous discharge and a translucent, taut and slightly concave tympanic membrane. Chronic changes include a roughened (cobblestone-like) appearance, ceruminous hyperplasia, cysts and polyps, thickening and stenosis, increased discharge, and tympanic membrane thickening and inflammation (myringitis), opacity, distortion and/or rupture.

Diagnostic imaging techniques include radiography, computed tomography (CT) and magnetic resonance imaging (MRI) (table 3). CT is the most cost-effective modality – the bone and soft-tissue windows with contrast enhancement give highly detailed information about ear canal inflammation and chronic changes (including thickening, ceruminous hyperplasia, stenosis and mineralisation), polyps and tumours, discharge, tympanic membrane integrity, otitis media and otitis interna.

Phases of treatment - induction and remission

Despite the complex multifactorial nature of otitis externa (see the PSPP system above), recurrent otitis externa can be regarded in its basic form as a progressive chronic inflammatory process. This is similar to canine atopic dermatitis (AD), where the pruritus and inflammation is the result of a complex immunologic cascade that varies at different stages of the condition as well as between breeds and individual dogs[13]. Moreover, canine AD is the most frequent primary factor in recurrent otitis externa factors[7,8].

Management recommendations for canine AD have evolved to consider this process and now recognise two distinct phases of treatment:

1. *Phase 1 reactive therapy* – the treatment of existing acute and/or chronic lesions and/or infection to clinical remission.
2. *Phase 2 proactive therapy* – long-term regular therapy to maintain remission and prevent flares.

Clinicians must understand the precise mode of action and spectrum of activity of the different treatment options for otitis to optimise treatment for an individual patient at each stage of their disease[14]. In contrast, inappropriate use of medication and/or a failure to move from induction to maintenance will increase the risk of treatment failure and progression to medically irreversible chronic otitis.

The therapeutic options for otitis can be grouped into antimicrobials, ear cleaning and anti-inflammatory treatments. These are considered below, emphasising the appropriate choices for induction and maintenance therapy.

When is an infection not an infection? When it's a dysbiosis

Cytology and culture studies have shown that most ear infections are associated with *Malassezia* yeasts, *Staphylococcus pseudintermedius* or *Pseudomonas aeruginosa*[14]. However, traditional sample and culture methods favour a limited number of easily isolated organisms[15,16]. High-throughput genomic sequencing techniques have revolutionised our understanding by revealing the rich complex microbial population of the ear canals and the dynamic changes seen in otitis.

The ear canal microbiome is a mix of bacterial and fungal microbiotas. Microbiomes vary between individuals but diversity seems to be key[16]. Diversity reflects the richness (i.e. the

total number of microbial species present) and evenness (i.e. the relative abundance of each species in the microbial community) of the microbial population[16].

The bacterial microbiota of canine ear canals shows high diversity with several abundant phyla, including Proteobacteria, Actinobacteria, Firmicutes, Fusobacteria and Bacteroidetes[16-19]. Inflamed ears show lower species richness (diversity) with approximately 70% showing a bacterial, 16% a fungal overgrowth and 7% a mixed overgrowth[16]. The most important organisms are *Malassezia pachydermatis*, *Staphylococcus pseudintermedius*, and *Staphylococcus schleiferi*, but more unusual organisms not previously implicated in otitis include anaerobes (*Finegoldia magna*, *Peptostreptococcus canis*, and *Porphyromonas cangingivalis*) and *Ralstonia* species, whereas *E. coli* and some *Porphyromonas* (including *P. cangingivalis*) are abundant in healthy ears[16,18,20-22]. In contrast, one study found few differences between allergic and non-allergic German shepherd dogs[19] with Actinobacteria (especially *Macrococcus*) most abundant in non-allergic dogs and Proteobacteria (especially *Sphingomonas*) in allergic dogs.

The fungal microbiota is again rich, with up to 10 phyla identified in ears and skin, although it is dominated by *Malassezia* spp.[16,23]. Affected ears show a loss of diversity and shift to *Malassezia* yeasts but the relative abundance of different species may be as important as the diversity *per se*[23]. In dogs, *M. globosa* and *M. restricta* predominate on healthy skin whereas *M. pachydermatis* were associated with atopic skin[24]. More virulent *M. pachydermatis* have also been associated with otitis externa in dogs[25]. Differences in lipid dependency and altered lipid profiles in healthy and affected skin and ears may therefore influence population shifts. This may explain why some breeds and individuals are more prone to *Malassezia*-associated otitis than others. Manipulating lipid profiles to support less pathogenic *Malassezia* species/strains may be beneficial, but further studies are required.

Whether altered bacterial and fungal population structures (the varieties and relative abundance of bacterial and fungal genera and species) are a cause or effect of atopic dermatitis and/or otitis is unclear. Influences include disease status, inflammation, household, sex, body site and breed. There is likely to be mutual interaction between skin barrier function, cutaneous immunity and the microbiome[26]. Loss of diversity leads to staphylococcal, *Malassezia* and *Pseudomonas* spp. dominated populations[18]. Once these reach a critical threshold they may contribute to ongoing inflammation and epidermal changes through exclusion of less pathogenic organisms, expression of pro-inflammatory mediators, and (in some atopic individuals) sensitisation and specific IgE production[28]. Therefore, preserving microbiome diversity is a key part of long-term maintenance therapy. Interestingly, topical 2% chlorhexidine/2% miconazole treatment on the skin[21], topical mometasone in ears[28], and systemic glucocorticoid and ciclosporin[29] for the skin preserve fungal and bacterial microbiota diversity.

Cultures and antimicrobial susceptibility tests – are they useful in otitis externa?

Cultures and antimicrobial susceptibility tests (ASTs) are of limited benefit in otitis externa. Most cases are associated with *Malassezia*, *Staphylococcus* or *Pseudomonas* spp., which are easily differentiated on cytology (yeasts, cocci and rods respectively). Appropriate empirical treatment can then be selected. ASTs cannot be used to reliably select appropriate antimicrobials as the results are very poorly predictive of the response to topical treatment. The breakpoints used to determine sensitivity and resistant assume systemic treatment and are in µg/ml ranges – this does not reflect topical treatment which can achieve mg/ml concentrations in the ear canals[30,31]. Therefore, infections listed as resistant to antimicrobials in µg/ml concentrations can be sensitive at mg/ml concentrations, although

this isn't guaranteed with high level acquired resistance[31]. A sensitive result, moreover, does not guarantee treatment success as the laboratory AST will not reflect local factors that can affect efficacy (e.g. ongoing inflammation, discharge, biofilm, ear canal stenosis and other primary, predisposing and perpetuating factors).

Cultures may be help where precise identification is needed to select appropriate empirical therapy. An example would be where organisms with unusual morphology (e.g. coryneforms, cocco-bacilli, filaments, yeasts, hyphae etc.) are seen on cytology raising suspicion of rare infections (e.g. unusual bacteria, *Candida* yeasts, *Aspergillus* hyphae etc.) [32,33]. Specific risk factors for *Aspergillus* spp. include immunosuppression, otic foreign bodies and prior antibiotic use, which can be used to prompt cytology and culture[32]. Culture can also be used to differentiate rods when considering leave-in products containing florfenicol - this is effective against *E. coli*, *Klebsiella* and *Proteus* spp. etc. but not *Pseudomonas* spp.

Topical antimicrobials and antimicrobial stewardship

Antibiotic treatment guidelines often group the drugs into 1st, 2nd and 3rd lines choices. This reflects the importance of the antibiotics to human and veterinary healthcare. In 2019, The European Medicines Agency categorised all antimicrobials into 4 groups for use in animals: A – Avoid; B – Restrict; C – Caution; and D – prudence (https://www.ema.europa.eu/en/documents/report/infographic-categorisation-antibiotics-use-animals-prudent-responsible-use_en.pdf; last accessed 28 Dec 2022). Wherever possible, drugs in category D are used in preference to those in categories C, B and A (table 4). The aim is to reduce the selection pressure for AMR and preserve the efficacy of these drugs for the future.

However, this concept is based around systemic antibiotic treatment, which affects the whole bacterial microbiota and not just the site of infection. For example, today's multi-drug resistance (MDR) *E. coli* urinary tract infection could have been selected for by the course of antibiotics given last month for a skin infection. It is likely that topical treatment has less impact than systemic treatment as local application to confined sites such as the ear canals will result in less collateral damage to microbiomes at other sites. Nevertheless, antimicrobial stewardship is a professional responsibility and this may begin to influence topical treatment choices[4].

Antifungals of the azole (e.g. clotrimazole, miconazole or posaconazole), allylamine (terbinafine) and polyene (nystatin) classes are usually effective in *Malassezia* yeast associated otitis. However, clinically significant resistance to systemic and topical azole treatment is being reported[34].

Without better antimicrobial stewardship further selection for antibiotic and antifungal resistance is likely. One area of concern is using polyvalent topical ear medications that contain antibiotics and antifungals to treat otitis associated with *Malassezia* yeasts or bacteria only. Using cytology and more specifically targeted topical therapy will help improve antimicrobial stewardship. For example, Danish and other Nordic national treatment guidelines advise first line therapy with an antimicrobial cleanser and topical or systemic glucocorticoids in these cases[35]. In addition, diagnosing and managing the underlying factors driving the ear infections will reduce the need for repeated treatment.

294 ***Pseudomonas* infections**

295 *Pseudomonas* spp. ear infections are challenging – *Pseudomonas* spp. show widespread
296 inherent resistance, mutate and develop acquired resistance rapidly, and readily form
297 biofilms[36]. Chronic MDR and biofilm-associated infections can be very difficult to eliminate.
298 Most infections involve *Pseudomonas aeruginosa*, although other species can be isolated.
299 These are a type of common source infection (i.e. associated with exposure of susceptible
300 individuals to a fomite/vehicle or vector contaminated by an infectious organism)[37].
301 *Pseudomonas* spp. are common and widespread in any wet environment, which can include
302 wet outdoor habitats as well as indoor sources such as washing facilities, drains, water and
303 food bowls. Other reservoirs important in veterinary healthcare include improperly cleaned
304 and dried equipment, shampoos/ear cleaners, disinfectants, multi-dose vials and other
305 solutions[38]. In addition, some dogs carry their own *Pseudomonas* bacterial population where
306 conformation and other factors provide a suitable moist and protected habitat. Examples
307 include lip folds, facial or body folds, and perivulval folds.
308 Exposure to *Pseudomonas* species is likely to be frequent but ear infections are uncommon
309 and opportunistic, requiring specific risk factors that allow the *Pseudomonas* bacteria to
310 colonise and proliferate. Therefore, infections are secondary (see the PSPP discussion
311 above) and primary *Pseudomonas* bacterial otitis is rarely (if ever seen)[7]. The most common
312 primary causes are atopic diseases, followed by masses, endocrinopathies and autoimmune
313 disease. *Pseudomonas* associated otitis develops more quickly if there was a mass or
314 autoimmune disease, as compared with allergies and endocrinopathies[7].
315 Diagnosis of *Pseudomonas* bacterial otitis is straightforward – most present with a severe
316 suppurative otitis with rod bacteria and neutrophils on cytology. Biofilm (see below)
317 formation is common[36]. If necessary, the *Pseudomonas* spp. can be confirmed on culture

but remember that the AST results will be poorly predictive of the outcome to topical treatment (see above).

Pseudomonas bacterial otitis should be aggressively treated from the outset (table 5). The best chance of a good outcome is with the first round of treatment – multiple failed treatments select for MDR and biofilm formation. Topical therapy is generally more effective as systemic treatment may not adequately penetrate into the inflamed ear canals and lumen. However, systemic antibiotics may be necessary where topical treatment isn't feasible – in this case, the antibiotics should be selected on the basis of culture and AST using the highest safe doses possible to minimise the risk of treatment failure (especially in chronic otitis and/or with biofilms)[39]. Effective analgesia is essential – *Pseudomonas* bacterial otitis is usually very painful and failure to provide adequate pain relief will compromise effective topical treatment (as well as being unethical). NSAIDs should generally be avoided as many cases will require concurrent glucocorticoid therapy to manage primary and perpetuating problems – safe options in these cases include paracetamol (acetaminophen), tramadol, bedinvetmab and/or gabapentin.

It is essential that a thorough holistic approach is taken in these cases to address the infection alongside the primary, predisposing and perpetuating triggers for the otitis. Successful treatment needs an effective integrated approach. Complex cases may need referral to a specialist.

Epidermal migration and ear cleaning

Production and clearance of cerumen is normally in balance. Epidermal migration results in outward movement of desquamated cells, cerumen and debris from the tympanic membrane to the pinnae[14,40]. However, epidermal migration may be limited by excessively

hairy ear canals, and/or individual variation. In addition, epidermal migration breaks down in otitis allowing desquamated cells, cerumen and debris to build up. Ear cleaning is therefore essential in managing otitis[14,40]. In one study of a ceruminolytic/ceruminosolvent ear cleaner in erythroceruminous otitis, cleaning resulted in improved clinical and cytological scores, decreased debris, and altered lipid profiles[41]. The latter effect may promote a more diverse microbiome as a topical 'prebiotic'. However, using the correct ear cleaner and technique is important to avoid compromising the clinical outcome. Clinicians should therefore be familiar with the properties of ear cleaners and the pros and cons of ear cleaning techniques (tables 6 and 7).

Foaming ear cleaners containing carbamides lift debris off the ear canal surface and break up material to ease cleaning and flushing. However, dogs can find the sound and sensation disturbing so these are best used in-clinic prior to other procedures such as a deep ear flush.

Antimicrobial compounds in ear cleaners can retard microbial proliferation. Cleaners with isopropyl alcohol, parachlorometaxylenol (PCMX), chlorhexidine, hypochlorous acid and a low pH seem to be most effective[42-44]. TrisEDTA at 50mg/ml can show additive activity of with chlorhexidine, aminoglycosides and fluoroquinolones (see above). Inclusion of mono- and polysaccharides can reduce microbial adherence to keratinocytes[45].

Most ear cleaners are potentially ototoxic and few (aside from squalene[46]) are indicated for use with a ruptured tympanic membrane[14]. Alcohols and acids may also irritate inflamed or ulcerated ear canals.

Biofilms

Biofilms are common - they will form on virtually any non-shedding surface in wet or humid conditions[47]. Biofilms are complex and dynamic populations of microorganisms that adhere

366 to each other and to a substrate (including the skin and hairs in and around the pinnae and
367 ear canals). The microbial cells are embedded within a slimy extracellular matrix composed
368 of a complex array of polysaccharides, proteins, lipids and DNA. Cells in a biofilm are
369 physiologically distinct from planktonic cells (i.e. living in a liquid medium) of the same
370 organism. Subpopulations may differentiate to specialise in motility, matrix production,
371 nutrient sharing, and sporulation. This can make biofilms highly persistent and (from a
372 microbial point of view) successful strategies. Almost all microbes can form biofilms – they
373 are most common with *Pseudomonas* spp. in otitis[3], but can be seen with staphylococcal
374 spp., other bacteria and *Malassezia* yeasts[2].
375 The diagnosis of a biofilm is usually straightforward – they have a characteristic clinical feel
376 and appearance (see table 6 and figure 7). On modified Wright-Giemsa stained cytology (i.e.
377 rapid in-clinic stains) they form fine pink-cerise veil or net-like material embedding the
378 neutrophils and organisms (figure 8), although Periodic Acid Schiff (PAS)[48] can be used as a
379 more specific stain. However, optimising culture techniques to identify biofilm-forming
380 ability from clinical samples would help clinicians when planning treatment in cases where
381 the biofilm is not clinically or cytologically obvious[3].
382 Biofilms have a profound impact on treatment. Once established, they enable bacteria to
383 persistently colonise tissues, medical equipment (including otoscopes) and environments.
384 They are sheltered from environment factors, cleaning, disinfection and antimicrobials, and
385 innate and adaptive immunity. Exposure to sub-lethal antimicrobial concentrations within
386 biofilms selects for antimicrobial and disinfectant resistance, which can then spread within
387 and between populations. Some organisms within biofilms may also have altered
388 physiological susceptibility to antimicrobials (i.e. persister cells that show reversible
389 antimicrobial tolerance). This allows biofilm-associated infections to rapidly recrudesce

following treatment. It is therefore essential that all the biofim is removed from the ear canals, pinnae, hairs and other body sites (e.g. lip folds and body folds) at the start of treatment.

N-acetyl cysteine (NAC) can damage biofilms, lower the MIC and enhance the efficacy of systemic antibiotics. It therefore possible that NAC and similar anti-biofilm compounds may aid treatment of biofilm-associated infections in animals[2]. A commercially available trisEDTA-NAC solution may facilitate removal and treatment of biofilms in ear canals, although time should be left between this and topical antibiotics as an *in vitro* study found most interactions between NAC and enrofloxacin or gentamicin were indifferent to antagonistic[49]. Other compounds with potential anti-biofilm and antimicrobial activity include chlorhexidine, polihexanide, hypochlorous acid[44,50]and trisEDTA[2].

Reversing chronic pathological changes

As well as eliminating infection the aim of the induction phase of treatment is to reverse the acquired pathological changes and restore the normal ear canal structure and function. A good outcome cannot be achieved without this. Once in remission, long-term therapy is needed to maintain the improvement and prevent relapse.

This requires broad-spectrum anti-inflammatory treatment, which in effect means topical or systemic glucocorticoids. These must be given to remission before tapering (see table 8) – this may take 2-3 weeks and will induce steroid-associated adverse effects. Ciclosporin does not appear to be effective at reversing inflammatory changes but may be helpful for long-term maintenance. Semi broad- (e.g. oclacitinib) or narrow- (e.g. lokivetmab and antihistamines) spectrum agents have limited efficacy in otitis.

Avoiding pain and aversion

Otitis is often painful, especially where there is severe inflammation, *Pseudomonas* spp. infections, and/or ulceration. Without adequate analgesia, dogs quickly become aversive to ear cleaning and topical treatment. This greatly restricts effective options for managing the immediate otitis as well as long-term maintenance treatment. The need for analgesia must be assessed and addressed in each case. More recently, we've seen increased numbers of dogs that are resistant to topical treatment from the outset. This may be related to a lack of socialisation, veterinary experiences and training during the 2020 Covid-19 pandemic.

Topical leave-in products (florfenicol/terbinafine/mometasone furoate, florfenicol/terbinafine/betamethasone) can maintain therapeutically effective concentrations in the ear canals for up to 35 days. The products can have a significant impact on quality of life by giving a 'treatment holiday'[51]. However, they are potentially ototoxic, can trigger inflammation in the conjunctiva, and have been associated with neurogenic keratoconjunctivitis sicca[52]. In addition, florfenicol is not effective against *Pseudomonas* spp. and therefore these products are not appropriate for most cases of suppurative otitis.

Clinicians have a role in helping owners train their dogs to accept topical treatment. This can start in early life by advising new owners to build in ear manipulation etc. into play. Clinics can demonstrate safe and effective ear cleaning and therapy techniques through training, social media and websites. Re-training dogs to accept topical therapy is possible with a slow and gradual approach to desensitisation, analgesia, anti-anxiety medication, and high-value rewards.

Future anti-inflammatory and antimicrobial treatment options

There are several new approaches to managing infections and inflammation in skin and ears under development. Early results (especially *in vitro* studies) are encouraging, although more clinical trials are needed to confirm efficacy.

New technologies that may modulate inflammation and infection in the skin and ears include photobiomodulation (low level laser therapy/LLLT, ultraviolet and blue or red light with or without the prior application of photo-activated chemicals) [53-56] and cold plasma[57].

Bacteriophages are highly species specific anti-bacterial viruses. First discovered in the late 19th century they were used as antibacterial agents in the early to mid-20th century before being superseded by antibiotics. With the advent of MDR, there is now renewed intertest in bacteriophage therapy[58]. In a pilot study, specific anti-*Pseudomonas* phages cleared MDR ear infections in 10 dogs[59]. Biobanking phages with known efficacy will help reduce the delay in isolating phages specific to each infection. Another approach would be isolate and replicate broad-spectrum antibacterial phage proteins (bacteriolysins) in stable formulation for immediate use.

Other novel antimicrobial compounds include various essential plant oils and extracts[60-65], manuka honey[43], antimicrobial peptides[66,67], lactoferricin[68] and trisEDTA/monensin[69]. Early studies show good *in vitro* efficacy, although this can be more varied in the presence of mature biofilms[60]. Nevertheless, clinical studies have been limited and efficacy is more variable.

These approaches could become new and effective treatments for otitis. However, clinical studies have been limited by low numbers of dogs, inconsistent outcome data, and a tendency to focus on one aspect of the otitis (for example, steroids were not used in clinical trials of antimicrobial peptide and honey containing products). Further studies are clearly

required, but it is unlikely that any one of these novel options will become a ‘cure’ for otitis. Instead, they are likely to become further options to include in integrated treatment programmes that address the primary triggers, predisposing factors, perpetuating changes and secondary infections in each case.

Summary of treatment recommendations for otitis externa

Recurrent ear infections in dogs are always secondary. Topical treatment for each flare will be successful in the short term but repeated cycles of inflammation and infection will lead to chronic inflammatory changes, pain and aversion, and AMR. These will make the flares more frequent and harder to control. Eventually, the changes will be irreversible and the dog will need a TECA/LBO or ablative CO2 or diode laser surgery – clinicians should reflect on the fact that most TECA/LBO or laser surgery is avoidable.

To achieve a good long term outcome it is essential that all the underlying factors in each case are diagnosed and managed. This means that the primary condition must be diagnosed and managed, predisposing risks identified and (as far as possible) corrected, and perpetuating factors reversed.

Treatment must be planned in two phases:

- Induction to get the ears in remission; this may involve cleaning the ear with an appropriate technique and product, antimicrobial therapy, and topical or systemic glucocorticoids.
- Long-term maintenance therapy to prevent relapses; this may involve regular ear cleaning and topical glucocorticoids alongside therapy appropriate to the primary and predisposing problems in each case.

A better understanding of the triggers for recurrent otitis in dogs will help clinicians plan effective management regimens that will make a huge difference to the quality of life of their patients and their owners. For example, in one study of 59 dogs with recurrent *Malassezia* yeast otitis unresponsive to primary care, 91% of the affected ears responded to a single ear flush that was followed up with a holistic integrated management plan[70].

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Figure legends

Figure 1 – acute erythroceruminous otitis showing inflammation in an ear canal with erythema, vascular swelling and a ceruminous discharge. There is little to cellular proliferation or structural change. The inflammation should respond rapidly to topical and/or systemic glucocorticoids.

Figure 2 – chronic inflammation in an ear canal with hyperplastic changes in the epidermis, dermis and ceruminous/sebaceous glands (giving the rough 'cobblestone' appearance). This results in a failure of epidermal migration, increased discharge and stenosis. These changes will start to prevent resolution and left unchecked will eventually result in an end-stage ear. This will require more aggressive systemic glucocorticoid treatment to reverse.

Figure 3 – erythroceruminous otitis characterised by erythema and a ceruminous discharge. These cases are most commonly associated with *Malassezia* yeast or staphylococcal bacterial overgrowths.

Figure 4 – suppurative otitis with ulceration, a purulent discharge and biofilm formation (note the biofilm matted into the surrounding hairs). These cases usually involve a *Pseudomonas* spp. infection.

Figure 5 – end stage otitis in an American cocker spaniel with multiple ceruminous polyps completely occluding the ear canals. These glandular and cystic changes are less responsive to glucocorticoid therapy than the epidermal/dermal hyperplasia seen in other breeds.

Figure 6 – early perpetuating changes of nodular hyperplasia giving the ear canal a thickened 'cobblestone' appearance. This is the early warning that the dog has started to develop chronic otitis and should prompt treatment to reverse the changes.

Figure 7 – biofilm from a dog with otitis; note the characteristic dark colour with the tenacious and slimy texture.

Figure 8 – cytology of a biofilm with neutrophils and rod bacteria embedded in a net- or veil-like cerise substance (Rapi-Diff 2 stain & x100 magnification).

Tables

Table 1 – primary factors in otitis externa

Group	**Examples**	**Prevalence in otitis**
Hypersensitivity	Atopic dermatitis/food induced atopic dermatitis Cutaneous adverse food reactions Allergic or irritant contact reactions	Common Uncommon Uncommon; usually to topical medications and cleaners
Parasitic	*Otodectes cynotis*	Common (especially in young dogs)

	Demodex species	Uncommon; usually seen with generalised disease
Space occupying lesions	Ceruminous gland adenoma/adenocarcinoma, plasmacytoma and other tumours Inflammatory polyp	Common in older dogs Uncommon to rare
Endocrinopathies	Hyperadrenocorticism, hypothyroidism & hyperoestrogenism (Sertoli cell tumours)	Uncommon
Immunosuppression	Iatrogenic (e.g. glucocorticoid therapy, chemotherapy etc.) Primary immunodeficiency	Uncommon Rare
Miscellaneous	Foreign body (e.g. grass awn) Acquired scar tissue and stenosis	Common Uncommon
Congenital	Ear canal narrowing or atresia	Rare

729

730 *Table 2 – predisposing factors in otitis externa*

Anatomy & conformation	Hairy pinnae and/or ear canals Pendulous pinnae Increased density and altered physiology of ceruminous glands (cocker, especially American, spaniels)

	Narrow ear canals (Chinese shar pei) or atresia
Lifestyle and management	Swimming Over-cleaning (wetting, maceration, impaction of material deeper in the ear canals, iatrogenic damage) Routine plucking of hairs Hot & humid environments

731

732 *Table 3 – Comparison of diagnostic imaging techniques in otitis externa (CT – computed*

733 *tomography*

	Radiography	**CT**	**MRI**
Cost	Low	Moderate	High
Time	Moderate	Fast	Long
Restraint required	Sedation or anaesthesia	Sedation or anaesthesia	Anaesthesia
Positioning difficulty	+++	+	+
Specificity	Good	Good	Good (soft-tissues) to poor (bony structures)
Sensitivity	Poor	Good	Good (soft-tissues) to poor (bony structures)

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738 *Table 4 – Topical antibiotics in otic preparations listed according to the European Medicines*

739 *Agency categorisation of antibiotics for animal use*

A – Avoid	None licensed
B - Restrict	Fluoroquinolones Polymixin B
C – Caution	Aminoglycosides Florfenicol
D - Prudence	Fusidic acid

740

741 *Table 5 – General principles of treatment for Pseudomonas spp. otitis*

Thorough history & full clinical examination	Identify primary, predisposing & perpetuating factors	Start diagnostic steps & appropriate treatment This is essential – the infections are secondary to these factors
	Identify potential sources of *Pseudomonas* spp.	Eliminate & avoid
	Identify on-animal *Pseudomonas* spp. reservoirs	Clean with an effective antimicrobial Treat with a topical antibiotic Correct where feasible
Check for biofilm production	See text for diagnosis & treatment	

Thoroughly clean the ears	Perform a thorough and deep ear flush under general anaesthetic Start cleaning with an appropriate flushing, anti-biofilm and antimicrobial product (see below)	
Use an effective topical antimicrobial	First-line antibiotics in commercial polyvalent ear medications	Polymixin B Fluoroquinolones (e.g. orbifloxacin, marbofloxacin & enrofloxacin) Gentamicin
	Off-label[1] topical treatment using injectable solutions at full strength or diluted to a concentration of >1mg/ml in saline or trisEDTA	Anti-*Pseudomonas* penicillins and cephalosporins (ticarcillin-clavulanate, piperacillin-tazobactam, ceftazidime) Fluoroquinolones Aminoglycosides (amikacin, gentamicin, tobramycin)
	TrisEDTA	Shows additive activity with chlorhexidine, fluoroquinolones and minoglycosides[31,71]; in the author's practice 50mg/ml is required for most *Pseudomonas* bacterial isolates

	Silver sulfadiazine	Can be effective at 1%[72] Shows additive activity with fluoroquinolones and aminoglycosides May be antagonistic with trisEDTA[31]
Use culture to determine end of treatment	Small numbers of persistent *Pseudomonas* bacteria can be missed on cytology (especially in biofilms)	

1 - use of these antibiotics must be justified by failure of first line treatment options despite appropriate therapeutic approaches; full informed consent (including the risk or adverse effects) must be obtained prior to treatment with off-label and/or compounded medications.

Table 6 – Otic discharges and ear cleaners

Colour	Dark brown	Pale brown to grey	Pale brown to yellow	Yellow to green	Dark green to black
Consistency	Waxy and adherent	Waxy to seborrhoeic	Seborrhoeic to purulent	Purulent	Thick and slimy
Association[1]	Ceruminous otitis	*Malassezia* yeasts	Staphylococcal bacteria	*Pseudomonas* spp.	Biofilm
Ceruminolytic & ceruminosolvent activity[2]					50mg/ml TrisEDTA or 2% n-acetyl cysteine (NAC)
Surfactant & detergent flushing activity[3]					

1 – indication only and always confirm with cytology; 2 - oil and alcohol-based cleaners; 3 – water and detergent-based cleaners.

751 *Table 7 – ear cleaning techniques*

Technique	**Manual cleansing**	**Ear bulb**	**Ear flushing**
Advantages	Simple Can be done by owners Does not require sedation or anaesthesia	More vigorous and effective Can be done in conscious animals	The only way to thoroughly clean the ear canals (including the horizontal ear canals and tympanic membranes)
Disadvantages	Limited efficacy	Increased risk (including tympanic membrane rupture)	Requires a general anaesthetic (regional nerve blocks may be useful)[73]
Suitability	Routine at-home cleansing	In-clinic cleaning	Deep ear flush & clean

752

753 *Table 8 – Treatment options for chronic pathological inflammatory changes*

Early changes – ceruminous hyperplasia with stenosis; ear canals still pliable and mobile	Topical diester (e.g. hydrocortisone aceponate) or traditional[1] glucocorticoids (e.g. mometasone furoate, dexamethasone,	Daily to remission and then taper for maintenance Diester glucocorticoids preferred for maintenance due to their better safety profile[74]

	triamcinolone & betamethasone)	
Mild changes – ceruminous hyperplasia with early stenosis and loss of pliability; ear canals still mobile	Topical traditional glucocorticoids Prednisolone/prednisone or methyl-prednisolone	Daily to remission and then taper 1 (prednisolone)/0.8 (methyl-prednisolone) mg/kg/day to remission and then taper
Moderate changes – epidermal/dermal hyperplasia, some stenosis and reduced pliability; otoscopy still possible and ear canals mobile	Prednisolone/prednisone or methyl-prednisolone	1 (prednisolone)/0.8 (methyl-prednisolone) mg/kg/day to remission and then taper
Severe changes – epidermal/dermal hyperplasia, almost complete stenosis, limited pliability, and reduced mobility	Triamcinolone Dexamethasone Intramural depot glucocorticoid injections (40 mg/ml triamcinolone or 3 mg/ml dexamethasone)	0.8 mg/kg/day to remission & then taper 0.14 mg/kg/day to remission & then taper Three 0.05ml injections into the horizontal and vertical ear canals[75]

End-stage otitis - complete stenosis with fixed ear canals	Total ear canal ablation with lateral bulla osteotomy (TECA/LBO) CO2 or diode laser surgery[76]	In most cases these techniques are avoidable Laser surgery preserves the ear canals but availability may be limited

754 1 - Use of potent traditional glucocorticoids (e.g. triamcinolone and dexamethasone) has a
755 greater risk of adverse effects and (wherever possible) daily treatment should be for a
756 maximum of 14 days after which the frequency should be tapered.

757