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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 total ear canal ablation/lateral bulla osteotomy 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 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 2 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 hemorrhage, 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 etiology 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 the following:

- 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)**.

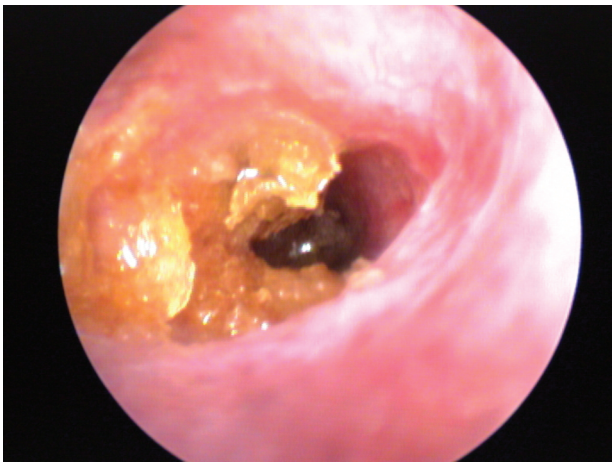

Figure 1—Acute erythroceruminous otitis showing inflammation in an ear canal with erythema, vascular swelling, and a ceruminous discharge. There is little cellular proliferation or structural change. The inflammation should respond rapidly to topical and/or systemic glucocorticoids.

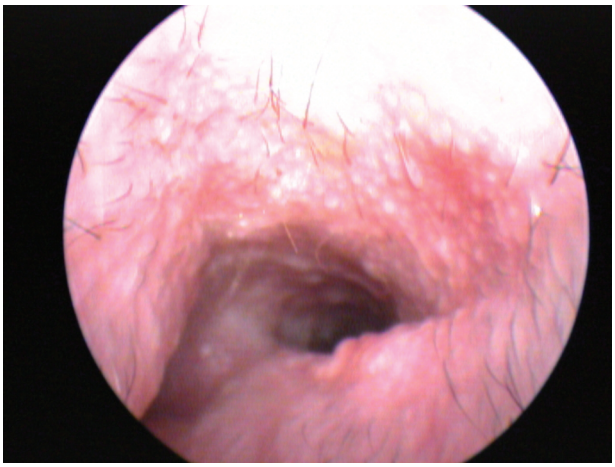

Figure 2—Chronic inflammation in an ear canal with hyperplastic changes in the epidermis, dermis, and ceruminous/sebaceous glands (giving the rough "cobblestone" appearance). This results in a failure of epidermal migration, increased discharge, and stenosis. These changes will start to prevent resolution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

There Are 2 Distinct Clinical Presentations of Otitis Externa

Most cases of otitis fall into 1 of 2 distinct clinical presentations:

- Erythroceruminous otitis: characterized by erythema with a ceruminous to seborrhoeic discharge **(Figure 3)**. The ears may simply be inflamed, but most cases are associated with *Malassezia* yeast or staphylococcal bacterial overgrowths; gram-negative bacteria are less common unless there is chronic inflammation and stenosis. These cases tend to be pruritic, but chronically inflamed ears can be painful.
- Suppurative otitis: characterized 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 being 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). Noninfected 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.

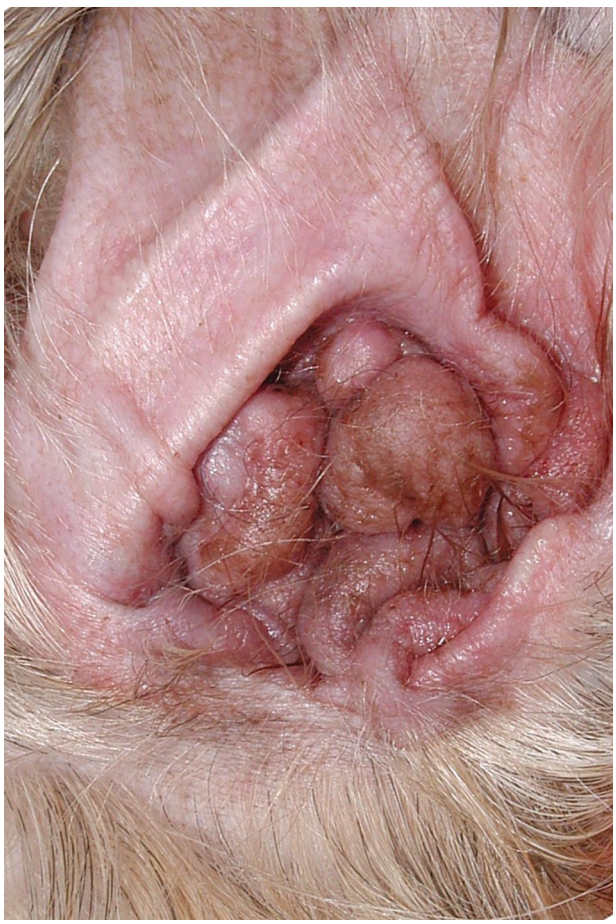

Figure 3—Erythroceruminous otitis characterized by erythema and a ceruminous discharge. These cases are most commonly associated with *Malassezia* yeast or staphylococcal bacterial overgrowth.

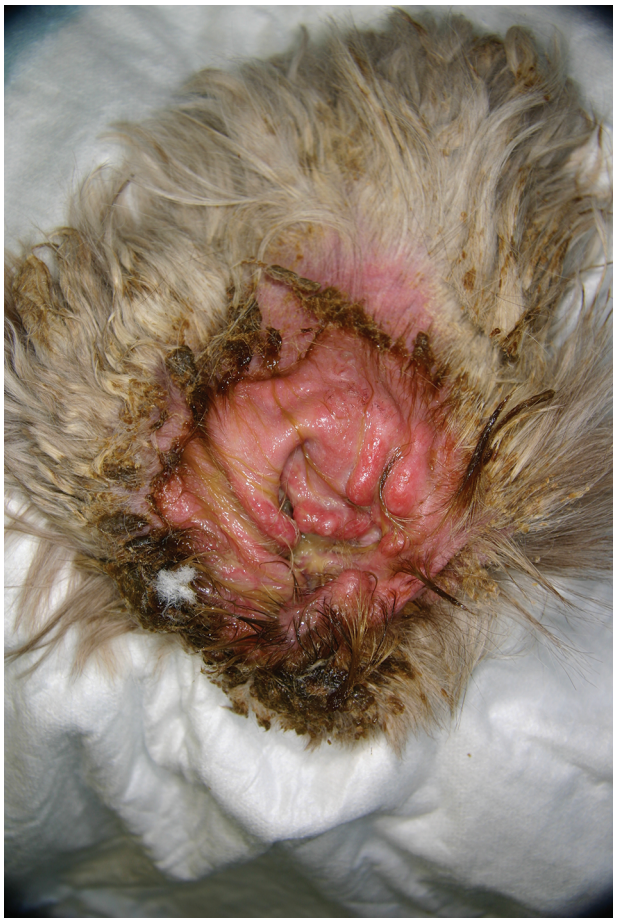

Figure 4—Suppurative otitis with ulceration, a purulent discharge, and biofilm formation (note the biofilm matted into the surrounding hairs). These cases usually involve a *Pseudomonas* spp infection.

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 are 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 secondary (S) infections[10] (see above).

Primary triggers in otitis externa

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

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 3-year-old Labrador Retriever with a history of recurrent bilateral erythroceruminous otitis with pruritus

Table 1—Primary factors in otitis externa.

Group	Examples	Prevalence in otitis
Hypersensitivity	Atopic dermatitis/food-induced atopic dermatitis	Common
	Cutaneous adverse food reactions	Uncommon
	Allergic or irritant contact reactions	Uncommon; usually to topical medications and cleaners
Parasitic	*Otodectes cynotis*	Common (especially in young dogs)
	Demodex species	Uncommon; usually seen with generalized disease
Space-occupying lesions	Ceruminous gland adenoma/adenocarcinoma, plasmacytoma, and other tumors	Common in older dogs
	Inflammatory polyp	Uncommon to rare
Endocrinopathies	Hyperadrenocorticism, hypothyroidism, and hyperoestrogenism (Sertoli cell tumors)	Uncommon
Immunosuppression	Iatrogenic (eg, glucocorticoid therapy, chemotherapy, etc)	Uncommon
	Primary immunodeficiency	Rare
Miscellaneous	Foreign body (eg, grass awn)	Common
	Acquired scar tissue and stenosis	Uncommon
Congenital	Ear canal narrowing or atresia	Rare

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 recognize 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 2 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 more local 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 **(Table 2)**.[9] 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 the rapid development of chronic changes (ie, 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 **(Figure 5)**.[11,12]

Chinese Shar Peis 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 to these dogs.

Table 2—Predisposing factors in otitis externa.

Category	Factor
Anatomy and 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
	Overcleaning (wetting, maceration, impaction of material deeper in the ear canals, iatrogenic damage)
	Routine plucking of hairs
	Hot and humid environments

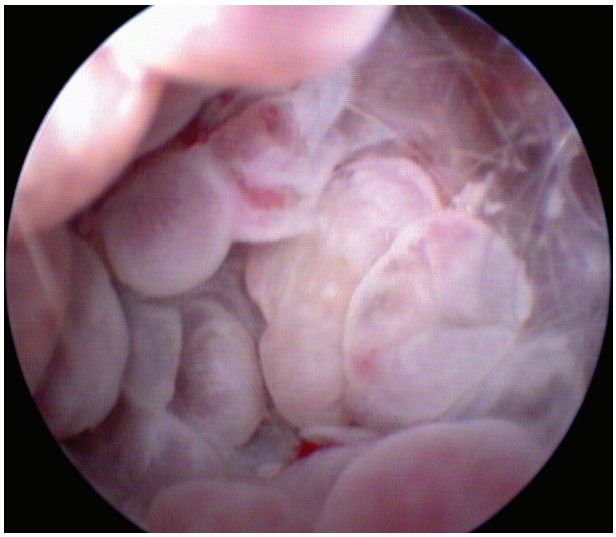

Figure 5—End-stage otitis in an American Cocker Spaniel with multiple ceruminous polyps completely occluding the ear canals. These glandular and cystic changes are less responsive to glucocorticoid therapy than the epidermal/dermal hyperplasia seen in other breeds.

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 (Figures 2 and **6**). Later changes include further epidermal and dermal hyperplasia and thickening, ear canal stenosis and occlusion, fibrosis, and mineralization. This can also

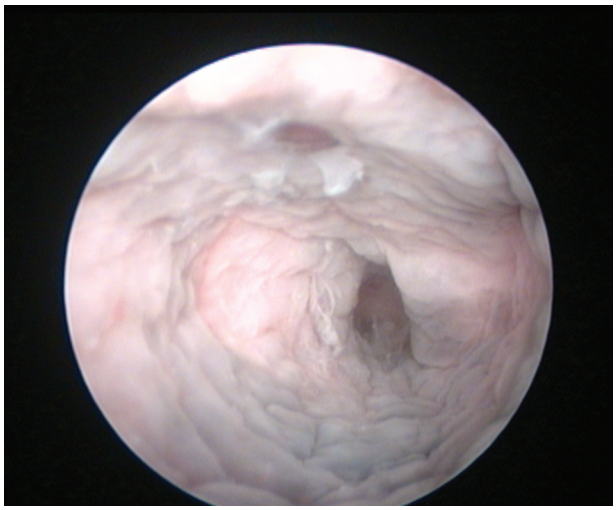

Figure 6—Early perpetuating changes of nodular hyperplasia giving the ear canal a thickened "cobblestone" appearance. This is the early warning that the dog has started to develop chronic otitis and should prompt treatment to reverse the changes.

result in tympanic membrane rupture, otitis media, and cholesteatoma formation.

It is essential that early chronic acquired pathological changes are recognized 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 to include a thorough assessment of their extent and severity. Traditionally, this has been based 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 mineralization), polyps and tumors, discharge, tympanic membrane integrity, otitis media, and otitis interna.

Table 3—Comparison of diagnostic imaging techniques in otitis externa.

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

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 are 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 recognize 2 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 optimize 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, emphasizing the appropriate choices for induction and maintenance therapy.

When Is an Infection Not an Infection? When It Is a Dysbiosis

Cytology and culture studies[14] have shown that most ear infections are associated with *Malassezia* yeasts, *Staphylococcus pseudintermedius*, or *Pseudomonas aeruginosa*. However, traditional sample and culture methods favor a limited number of easily isolated organisms.[15,16] High-throughput genomic sequencing techniques have revolutionized 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 (ie, the total number of microbial species present) and evenness (ie, 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 *Escherichia coli* and some *Porphyromonas* (including *P cangingivalis*) are abundant in healthy ears.[16,18,20–22] In contrast, 1 study[19] found few differences between allergic and nonallergic German Shepherd Dogs with Actinobacteria (especially *Macrococcus*) most abundant in nonallergic 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.[27] Once these reach a critical threshold, they may contribute to ongoing inflammation and epidermal changes through the exclusion of less pathogenic organisms, expression of proinflammatory mediators, and (in some atopic individuals) sensitization 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 resistance assume systemic treatment and are in microgram per milliliter ranges: this does not reflect topical treatments, which can achieve milligram per milliliter concentrations in the ear canals.[30,31] Therefore, infections listed as resistant to antimicrobials in microgram per milliliter concentrations can be sensitive at milligram per milliliter concentrations, although this is not 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 (eg, ongoing inflammation, discharge, biofilm, ear canal stenosis, and other primary, predisposing, and perpetuating factors).

Cultures may be helpful where precise identification is needed to select appropriate empirical therapy. An example would be where organisms with unusual morphology (eg, coryneforms, cocco-bacilli, filaments, yeasts, hyphae, etc) are seen on cytology raising suspicion of rare infections (eg, 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*, *Proteus* spp, etc, but not *Pseudomonas* spp.

Topical Antimicrobials and Antimicrobial Stewardship

Antibiotic treatment guidelines often group the drugs into first-, second-, and third-line choices. This reflects the importance of antibiotics to human and veterinary healthcare. In 2019, The European Medicines Agency categorized 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; accessed December 28, 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 multidrug 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

Table 4—Topical antibiotics in otic preparations listed according to the European Medicines Agency categorization of antibiotics for animal use.

Category	Antibiotics
A: avoid	None licensed
B: restrict	Fluoroquinolones Polymixin B
C: caution	Aminoglycosides Florfenicol
D: prudence	Fusidic acid

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 (eg, 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 ear infections will reduce the need for repeated treatment.

Pseudomonas Infections

Pseudomonas spp ear infections are challenging; *Pseudomonas* spp show widespread inherent resistance, mutate and develop acquired resistance rapidly, and readily form biofilms.[36] Chronic MDR and biofilm-associated infections can be very difficult to eliminate.

Most infections involve *Pseudomonas aeruginosa*, although other species can be isolated. These are a type of common source infection (ie, associated with exposure of susceptible individuals to a fomite/vehicle or vector contaminated by an infectious organism).[37] *Pseudomonas* spp are common and widespread in any wet environment, which can include wet outdoor habitats as well as indoor sources such as washing facilities, drains, water, and food bowls. Other reservoirs important in veterinary healthcare include improperly cleaned and dried equipment, shampoos/ear cleaners, disinfectants, multidose vials, and other solutions.[38] In addition, some dogs carry their own *Pseudomonas* bacterial population where conformation and other factors provide a suitable moist and protected habitat. Examples include lip folds, facial or body folds, and perivulval folds.

Exposure to *Pseudomonas* species is likely to be frequent, but ear infections are uncommon and opportunistic, requiring specific risk factors that allow the *Pseudomonas* bacteria to colonize and proliferate. Therefore, infections are secondary (see the PSPP discussion above) and primary *Pseudomonas* bacterial otitis is rarely (if ever seen).[7] The most common primary causes are atopic diseases, followed by masses, endocrinopathies, and autoimmune diseases. *Pseudomonas*-associated otitis develops more quickly if there was a mass or autoimmune disease, as compared with atopic disease and endocrinopathies.[7]

Diagnosis of *Pseudomonas* bacterial otitis is straightforward; most present with a severe suppurative otitis with rod bacteria and neutrophils on cytology. Biofilm (see below) 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 of 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 the inflamed ear canals and lumen. However, systemic antibiotics may be necessary where a topical treatment is not feasible; in this case, the antibiotics should be selected on the basis of culture and AST using the highest safe doses possible to minimize 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 thoroughly 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 a referral to a specialist.

Epidermal Migration and Ear Cleaning

Production and clearance of cerumen are normally in balance. Epidermal migration results in the 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 1 study[41] of a ceruminolytic/ceruminosolvent ear

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

General principles of treatment	Instructions	Instructions
Thorough history and full clinical examination	Identify primary, predisposing, and perpetuating factors	Start diagnostic steps and appropriate treatment This is essential; the infections are secondary to these factors
	Identify potential sources of *Pseudomonas* spp	Eliminate and 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 and treatment	
Thoroughly clean the ears	Perform a thorough and deep ear flush under general anesthetic Start cleaning with an appropriate flushing, antibiofilm, and antimicrobial product (see below)	
Use an effective topical antimicrobial	First-line antibiotics in commercial polyvalent ear medications	Polymixin B Fluoroquinolones (eg, orbifloxacin, marbofloxacin, and enrofloxacin) Gentamicin
	Off-label[a] topical treatment using injectable solutions at full strength or diluted to a concentration of > 1 mg/mL in saline or Tris-EDTA	Anti-*Pseudomonas* penicillins and cephalosporins (ticarcillin-clavulanate, piperacillin-tazobactam, and ceftazidime) Fluoroquinolones Aminoglycosides (amikacin, gentamicin, and tobramycin)
	Tris-EDTA	Shows additive activity with chlorhexidine, fluoroquinolones, and aminoglycosides[31,71]; in the author's practice 50 mg/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 Tris-EDTA[31]
Use culture to determine end of treatment	Small numbers of persistent *Pseudomonas* bacteria can be missed on cytology (especially in biofilms)	

[a]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.

cleaner in erythroceruminous otitis, cleaning resulted in improved clinical and cytological scores, decreased debris, and altered lipid profiles. 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, chlorhexidine, hypochlorous acid, and a low pH seem to be most effective.[42–44] Tris-EDTA at 50 mg/mL can show additive activity with chlorhexidine, aminoglycosides, and fluoroquinolones (see above). The inclusion of mono- and polysaccharides can reduce microbial adherence to keratinocytes.[45]

Table 6—Otic discharges and ear cleaners.

Discharge/cleaner	Description				
Color	Dark brown	Pale brown to gray	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[a]	Ceruminous otitis	*Malassezia* yeasts	Staphylococcal bacteria	*Pseudomonas* spp	Biofilm
Ceruminolytic and ceruminosolvent activity needed[b]	+++	++	+	-	50 mg/mL Tris-EDTA or 2% NAC
Surfactant and detergent flushing activity needed[c]	-	+	++	+++	

[a]Indication only and always confirm with cytology. [b]Oil and alcohol-based cleaners. [c]Water and detergent-based cleaners.

Table 7—Ear cleaning techniques.

Technique	Manual cleansing	Ear bulb	Ear flushing
Advantages	Simple Can be done by owners Does not require sedation or anesthesia	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 anesthetic (additional regional nerve blocks may be useful)[73]
Suitability	Routine at-home cleansing	In-clinic cleaning	Deep ear flush and clean

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 nonshedding surface in wet or humid conditions.[47] Biofilms are complex and dynamic populations of microorganisms that adhere to each other and to a substrate (including the skin and hairs in and around the pinnae and ear canals). The microbial cells are embedded within a slimy extracellular matrix composed of a complex array of polysaccharides, proteins, lipids, and DNA. Cells in a biofilm are physiologically distinct from planktonic cells (ie, living in a liquid medium) of the same organism. Subpopulations may differentiate to specialize in motility, matrix production, nutrient sharing, and sporulation. This can make biofilms highly persistent and (from a microbial point of view) successful strategies. Almost all microbes can form biofilms; they are most common with *Pseudomonas* spp in otitis[3] but can be seen with *Staphylococcus* spp, other bacteria, and *Malassezia* yeasts.[2]

The diagnosis of biofilms is usually straightforward; they have a characteristic clinical feel and appearance (see Table 6 and **Figure 7**). On modified Wright-Giemsa stained cytology (ie, rapid in-clinic stains), they form a fine pink-cerise veil or net-like material embedding the neutrophils and organisms **(Figure 8)**, although periodic acid Schiff[48] can be used as a more specific stain. However, optimizing culture techniques to identify biofilm-forming ability from clinical samples would help clinicians when planning treatment in cases where the biofilm is not clinically or cytologically obvious.[3]

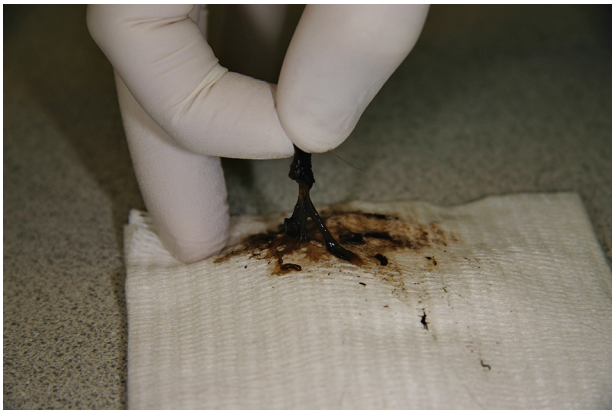

Figure 7—Biofilm from a dog with otitis; note the characteristic dark color with the tenacious and slimy texture.

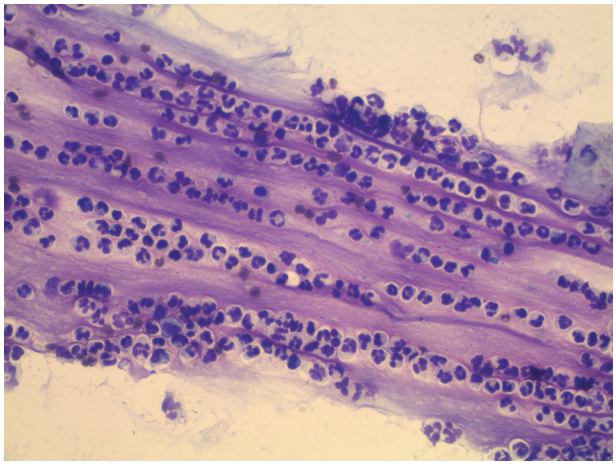

Figure 8—Cytology of a biofilm with neutrophils and rod bacteria embedded in a net- or veil-like cerise substance (Rapi-Diff 2 stain and 100X magnification).

Biofilms have a profound impact on treatment. Once established, they enable bacteria to persistently colonize tissues, medical equipment (including otoscopes), and environments. They are sheltered from environmental factors, cleaning, disinfection, antimicrobials, and innate and adaptive immunity. Exposure to sublethal antimicrobial concentrations within biofilms selects for antimicrobial and disinfectant resistance, which can then spread within and between populations. Some organisms within biofilms may also have altered physiological susceptibility to antimicrobials (ie, persister cells that show reversible antimicrobial tolerance). This allows biofilm-associated infections to rapidly recrudesce following treatment. It is therefore essential that all the biofilm is removed from the ear canals, pinnae, hairs, and other body sites (eg, 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 antibiofilm compounds may aid the treatment of biofilm-associated infections in animals.[2] A commercially available Tris EDTA-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[49] found most interactions between NAC and enrofloxacin or gentamicin were indifferent to antagonistic. Other compounds with potential anti-biofilm and antimicrobial activity include chlorhexidine, polihexanide, hypochlorous acid,[44,50] and Tris-EDTA.[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 **(Table 8)**; this may take 2 to 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 (eg, oclacitinib)- or narrow (eg, 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 immediate otitis as well as long-term maintenance treatment. The need for analgesia must be assessed and addressed in each case. More recently, we have seen increased numbers of dogs that are resistant to topical treatment from the outset. This may be related to a lack of socialization, 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 into play. Clinics can demonstrate safe and effective ear cleaning and therapy techniques through training, social media, and websites. Retraining dogs to accept topical therapy is possible with a slow and gradual approach to desensitization, 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

Table 8—Treatment options for chronic pathological inflammatory changes.

Changes	Treatment options	Instructions
Early changes: ceruminous hyperplasia with stenosis; ear canals still pliable and mobile	Topical diester (eg, hydrocortisone aceponate) or traditional[a] glucocorticoids (eg, mometasone furoate, dexamethasone, triamcinolone, and betamethasone)	Daily to remission and then taper for maintenance Diester glucocorticoids preferred for maintenance due to their better safety profile[74]
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/d 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/d 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/d to remission and then taper 0.14 mg/kg/d to remission and then taper Three 0.05-mL 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) CO_2 or diode laser surgery[76]	In most cases, these techniques are avoidable Laser surgery[b] preserves the ear canals but availability may be limited

[a]Use of potent traditional glucocorticoids (eg, triamcinolone and dexamethasone) has a greater risk of adverse effects, and (wherever possible) daily treatment should be for a maximum of 14 days after which the frequency should be tapered. [b]Laser surgery can also be used in the severe changes category.

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, ultraviolet, and blue or red light with or without the prior application of photoactivated chemicals)[53–56] and cold plasma.[57]

Bacteriophages are highly species-specific antibacterial 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 interest in bacteriophage therapy.[58] In a pilot study,[59] specific anti-*Pseudomonas* phages cleared MDR ear infections in 10 dogs. Biobanking phages with known efficacy will help reduce the delay in isolating phages specific to each infection. Another approach would be to isolate and replicate broad-spectrum antibacterial phage proteins (bacteriolysins) in a 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 Tris-EDTA/monensin.[69] Early studies[60] show good in vitro efficacy, although this can be more varied in the presence of mature biofilms. 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 programs 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 CO_2 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 the 2 following 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 1 study[70] 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.

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