Multi-Drug-Resistant Gram-Negative Otitis

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Introduction

Ear infections associated with resistant gram-negative bacteria are among the most challenging and frustrating diseases in veterinary medicine. These infections usually present clinically as chronic malodorous suppurative otitis externa and often with associated otitis media. The issue with these infections is not only finding effective topical and systemic medications to successfully kill the bacteria. Of equal importance is the need for aggressive early diagnostics and treatment to minimize and reverse chronic changes in the ear canal, to treat long enough and deep enough until the existing infection is controlled, and to realize that long-term management of an ear canal that will never again be normal is required.

As with all types of otitis, gram-negative bacteria colonize and infect the ear canal secondary to predisposing and/or primary factors with the most common being breed conformation characteristics, ear canal obstruction (masses, foreign bodies, ceruminoliths, etc.), hypersensitivities (atopic disease, cutaneous adverse reactions to food), cornification/glandular disorders, and parasites. Chronic moisture associated with swimming may act as a predisposing and a perpetuating factor in patients with chronic gram-negative otitis.

*Pseudomonas aeruginosa* is the most common and most resistant gram-negative bacteria associated with otitis in dogs. Other gram-negative bacteria of otic importance include *Escherichia coli* and *Proteus* spp., *Pasteurella* spp., *Klebsiella* spp., *Citrobacter* spp., and *Enterobacter* spp. are less common gram-negative bacterial isolates. Although the subject of this presentation is resistant gram-negative otitis, mixed infections are common and usually composed of *Staphylococcus pseudintermedius* along with a gram-negative rod.

Diagnosis

Clinical findings. Gram-negative otitis typically presents with an erythematous, edematous, malodorous suppurative otitis externa. *Pseudomonas* has a typical foul-smelling, greenish-yellow to gray discharge. Affected ears are painful and erosions, ulcerations, and hemorrhage are often present. Epidermal and glandular hyperplasia, fibrosis, narrowing of the canal, and calcification are seen with chronicity. Otitis media from extension of infection from the horizontal canal through the tympanic membrane has been reported in over 80% of chronic gram-negative otitis cases in dogs.
**Ear canal cytology.** Cytology is performed with a cotton-tipped applicator in all cases of otitis. Samples should be taken from the horizontal canal being careful not to rupture an intact tympanic membrane. Chronic resistant gram-negative otic infections have a high prevalence of otitis media. These patients also need a cytology sample taken from the middle ear using swabs made for small body cavities (Puritan Sterile Calcium Alginate Nasopharyngeal Tip Swabs, Puritan) or material from the tip of the catheter or needle used to perform a myringotomy. Cytology associated with gram-negative otitis is characterized by a predominant population of rods with neutrophils, phagocytized bacteria, red blood cells, and proteinaceous debris. Mixed infections may also be present with coccoid bacteria and yeast. Topical treatments can usually be selected empirically based on morphology of the organisms, especially in cases of acute otitis externa. Repeat cytology at recheck visits is the only way to monitor response to prescribed treatments.

**Bacterial culture and susceptibility testing.** Culture and susceptibility testing (CS) is not indicated for cases of acute otitis externa to be treated with anti-inflammatory drugs, ear cleaning, and topical antimicrobials alone. It is indicated for severe chronic cases of otitis externa, when rods and inflammatory cells are found on cytology, when otitis media is present, when systemic antibiotics are deemed necessary, and in cases not responding to empirical therapy. The sample should be taken from the middle ear (when otitis media is present) and/or deep within the horizontal canal using a sterile culturette passed through a sterile otoscope cone before cleaning or treatment. Even when CS is indicated, variable results may be obtained due to interference by concurrent antibiotic use, sample location, multiple strains of the same organism present in the ear canal, and variability among laboratories. Culture and susceptibility results are not reproducible 100% of the time in samples taken from a badly infected ear canal or tympanic bulla.

In a prospective study (Cole et al., 1998) of 23 dogs with chronic bilateral otitis externa of at least 6-months’ duration, concurrent otitis media was present in at least one tympanic bulla in 22 of the dogs (38 of 46 ears). *Pseudomonas* spp. was found in 26.3% and 36.8%, *Proteus* spp. in 10.5% and 13.2%, and *Citrobacter* spp. in 2.6% and 2.6%, of horizontal ear canals and middle ears, respectively. *Escherichia coli* was found in 5.3% of middle ears only. *Pseudomonas* spp. isolated from the horizontal ear canal had different susceptibility profiles from those isolated from the middle ear in 76.3% of the ears. Thus when CS is indicated, samples should be taken from the horizontal ear canal and middle ear for a more definitive evaluation. Antimicrobial susceptibility testing of the *Pseudomonas* spp. isolates revealed susceptibility to enrofloxacin 12.5% and 35.0%, gentamicin 56.3% and 60.0%, neomycin 0% and 11.1%, polymyxin B 100% and 95.0%, and tobramycin 85.7% and 88.2%, for isolates from the horizontal canal and middle ear, respectively. Of the 38 ears evaluated, a difference in total number of isolates or susceptibility patterns between organisms from the horizontal ear canal and middle ear was found in 34 (89.5%) ears.

The above-referenced study was published in 1998. Unfortunately, to the author’s knowledge there have been no new prospective studies published which have evaluated gram-negative pathogens from the middle ear since that time. A retrospective study (Palmeiro et al., 2004) was conducted on 44 dogs with chronic otitis media (duration of ear canal disease 24.9 ± 21.6 months) presented to the University of Pennsylvania School of Veterinary Medicine. Ninety
tympanic bullae were sampled during the course of the study. Pseudomonas aeruginosa was isolated in 43% of the samples, Enterococcus spp. in 16%, Proteus spp. in 13%, and E. coli in 7%. Very limited susceptibility data were reported with 18% of the P. aeruginosa isolates susceptible to enrofloxacin and 56% susceptible to ciprofloxacin.

Treatment

Basic principles. The same basic principles of treating otitis apply to gram-negative infections:

1) Identify and treat predisposing and primary factors, especially atopic dermatitis, food allergy, scaling/glandular abnormalities and swimming.

2) Use topical and systemic glucocorticoids to increase patency of a stenotic ear canal before attempting full examination and flushing:
   - Topical betamethasone, mometasone, triamcinolone, dexamethasone or fluocinolone/DMSO (Synotic, Zoetis): twice a day for 1-2 weeks
   - Triamcinolone: 0.1 mg/kg total dose injected in a ring-like fashion into the lining of the ear canal
   - Systemic dexamethasone: 0.1 mg/kg, IM or SQ
   - Prednisone or prednisolone: 0.5-2.0 mg/kg/day for 1-2 weeks

3) Completely clean and flush the ear canal and tympanic bulla (if indicated) initially and keep the ear clean forever after. The reader is directed to other references (Gotthelf, 2004; Logas, 2009) which describe in detail initial cleaning and flushing of the external ear and tympanic bulla. Depending on the nature of the otic exudate, condition of the ear canal, and integrity of the tympanic membrane, various agents may be utilized for in-hospital or at-home cleaning, some of which contain ingredients which also help with gram-negative bacterial pathogens.

   - For in-clinic flushing under general anesthesia, especially when lavage of the tympanic bulla is indicated, copious amounts of warm water, saline and tris-EDTA (T8 Solution, Bayer; TrizEDTA, Dechra) are all good choices. Tris-EDTA has been safely used in middle ears and offers the advantage of destabilizing and increasing permeability of gram-negative bacterial cell walls. Other flushing solutions include chlorhexidine (2% solution diluted 1:40 with water), dilute povidone iodine (dilute 1:50 with water with an intact tympanic membrane or 1:100 if perforated), and dilute acetic acid (5% white vinegar diluted 1:1 to 1:3 with water). Although chlorhexidine has broad-spectrum antimicrobial activity, Pseudomonas and other gram-negative bacteria may be resistant at concentrations of 0.2% and lower. Additionally, chlorhexidine may be ototoxic and should be used with caution with ruptured tympanic membranes. Chlorhexidine is also a difficult molecule to formulate correctly and it is advised not to compound other ingredients into commercial formulations of chlorhexidine or risk it losing activity. A 2% solution of acetic acid has been demonstrated to be effective in vitro against Pseudomonas with as little as 1 minute contact time but may cause irritancy in some ears at this and higher concentrations. Pre-soaking the ear with a ceruminolytic agent containing carbamide or urea peroxide and dioctyl sodium sulfosuccinate is necessary...
with tenacious ceruminous exudate. The ceruminolytic should be cleaned from the ear during the flushing procedure due to potential ototoxicity.

- While the otic infection is being treated and for long-term maintenance and prophylaxis, the ear canal must continue to be cleaned. Chronic gram-negative infections cause changes to the anatomy and physiology of the ear canal which predispose to recurrence. Commercial products may contain combinations of mild surfactants to help remove debris. Many products contain acids to lower the pH of the ear canal to prevent microbial overgrowth and infection (Epi-Otic, Virbac; MalAcetic Otic, Dechra; OtiRinse, Bayer). Other cleaners are more neutral in pH but contain broad-spectrum antiseptics, anti-adhesive monosaccharide technology, tris-EDTA and other ingredients to control recurrence of infection without acidification (Duoxo Micellar Solution, Sogeval; Epi-Otic Advanced, Virbac; T8 Keto Flush, Bayer; TrizULTRA + Keto Otic Flush, Dechra; Zymox Otic, Pet King Brands). Cleaners may be needed as frequently as every 12 hours initially but should eventually be used as infrequently as possible to clean and control infection without causing maceration of the lining of the ear canal. For dogs that cannot be completely kept out of the water and have problems with recurrent gram-negative infections, the combination of aluminum acetate (acidifier/astringent) and 1% hydrocortisone (CortAstrin, HB 101, HydroPlus; generics available through veterinary distributors) works well applied after swimming and as needed between swimming.

4) If at all possible, eliminate swimming.

5) Use a sufficient volume of topical medication to fill the ear canal and bulla:
   - 0.25-1.5 mL, q12-24h
   - Use a syringe

6) Continue antimicrobial treatments for 2 weeks after the infection is cytologically resolved.

7) Utilize a long-term maintenance program to prevent recurrence.

8) Consider a surgical option for an ear that cannot be medically salvaged.

Topical antimicrobials. In an evidence-based review (Nuttall et al., 2007) of interventions for treatment of *Pseudomonas* otitis in dogs between 1967 and 2006, the authors concluded that there was insufficient evidence for or against recommending the use of any of the treatments evaluated! So, as one might conclude, recommendations for the treatment of gram-negative otitis are largely based on *in vitro* data and clinical experience.

Topical antimicrobials are mandatory and chosen based on clinical and cytologic findings (rods, cocci, yeast). Culture and susceptibility results may also help guide selection of topical treatments. However, CS typically underestimates *in vivo* efficacy of topicals since topical antibiotics are used at concentrations many times those attainable in plasma and tissues and are often compounded with vehicles that enhance the efficacy of the antibiotic. Based on CS (as reviewed above) and/or clinical experience with resistant gram-negative infections the following
antibiotics have been utilized topically in commercial combination formulations or compounded with other ingredients:

- Neomycin, gentamicin
- Enrofloxacin, marbofloxacin, ciprofloxacin, orbifloxacin
- Silver sulfadiazine
- Polymyxin B
- Amikacin
- Tobramycin
- Ticarcillin/clavulanic acid
- Ceftazadime
- Carbapenems

Some commercial formulations (Mometamax, Otomax, Posatex, Merck) are in oil-containing vehicles. While they adhere well to the lining of the ear canal, they may occlude and further moisturize an already macerated epithelium and not penetrate the entire length of the canal. If the ointment or suspension does enter the middle ear, it is uncertain how long it takes for normal metabolic processes to remove it. In moist ears and in ears with ruptured tympanic membranes, commercial formulations (Baytril Otic, Bayer; Gentocin Otic, Various; Surolan, Vetoquinol; Tresaderm, Merial) or compounded formulations with water-soluble vehicles are more desirable. All of the current commercial veterinary otic formulations in the United States are approved for otitis externa but not otitis media. Clinical experience and data from other species suggest that the fluoroquinolones are tolerated in the middle ears of dogs and, therefore, a compounded fluoroquinolone, tris-EDTA, and steroid aqueous preparation is often instilled into the tympanic bulla after a middle ear flush. Polymyxin B and the aminoglycosides are potentially ototoxic so should be used with care with otitis media. They will also lose activity in an environment with purulent debris.

Vehicles for compounded topical antibiotics have included water, distilled water, sterile water, sterile saline, tris-EDTA (as a vehicle or applied 15-30 minutes before the antibiotic), and aluminum acetate/hydrocortisone. Topical antibiotics have typically been compounded at concentrations of 1-2% (10-20 mg/mL) or higher. Stability data are lacking on most compounded formulations.

It is absolutely critical that a sufficient quantity of medication be used in an ear to treat the entire external ear canal and the tympanic bulla with otitis media. This means 0.25-0.50 mL in small dogs to as much as 1.00-1.50 mL in large breeds, generally applied every 12 hours. Treatment should be continued for 2 weeks after negative cytology followed by initiation of a maintenance program to prevent recurrence.

Systemic antimicrobials. Systemic antimicrobial therapy for infectious otitis externa and otitis media is controversial. Some dermatologists have stated that there is not a difference in success rate managing otitis with or without systemic antibiotics. However, there are no credible data comparing efficacy for chronic otitis externa or otitis media using topical therapy alone versus topical and systemic treatments. Most dermatologists use systemic antibiotics based on CS
results in patients with otitis media, severe proliferative chronic otitis externa, purulent ulcerative otitis externa, and when owners cannot treat their pet’s ears with topical therapy.

The dilemma is that the only class of oral antibiotics that may be efficacious for resistant *Pseudomonas* is the fluoroquinolones.

- Enrofloxacin 5-20 mg/kg, q24h, PO
- Marbofloxacin 2.75-5.5 mg/kg, q24h, PO
- Ciprofloxacin 25-30 mg/kg, q24h, PO

Even when susceptible, the quinolones should be used at the high end of the flexible dosing range. Ciprofloxacin should only be used when CS indicates resistance to the veterinary-approved drugs but continued susceptibility to ciprofloxacin based on MIC’s. Even in this situation, oral ciprofloxacin tablets may not achieve effective plasma and tissue concentrations because of extremely variable absorption after oral administration in dogs (Papich, 2012).

When *Pseudomonas* has become multi-drug resistant and topical therapy alone does not resolve the infection, parenteral antibiotic treatment is required. Options in dogs based on CS generally include ticarcillin-clavulanate potassium (15-25 mg/kg, q8h, IV), meropenem (12 mg/kg, q8h, SQ; 24 mg/kg, q8h, IV), ceftazidime (30 mg/kg, q6h, IV, IM; 30 mg/kg, q4h, SQ), amikacin (15-30 mg/kg, q24h, IM, SQ, IV), and gentamicin (10-14 mg/kg, q24h, IM, SQ, IV). Patients on the aminoglycosides must be monitored for nephrotoxicity with urinalysis for protein and tubular casts and serum for BUN and creatinine every 1-2 weeks. Meropenem and ceftazidime should be used as a last resort due to implications for human health.

**Duration of treatment.** Chronic resistant gram-negative otitis, especially with middle ear involvement, requires weeks to months of continual treatment followed by a permanent maintenance program to prevent recurrence of infection. Specific antimicrobial treatment should be continued for 2 weeks after negative cytology.

In the retrospective study (Palmeiro et al, 2004) discussed above, the 44 dogs with chronic otitis media were treated with lavage of the tympanic bulla (100%) with sterile saline or saline with a mild ceruminolytic, appropriate systemic antimicrobials (91%) based on CS (antibiotics) or empirically (antifungals), topical and/or systemic steroids (58%), otic cleansers (100%), and topical antimicrobials (100%) based on cytology. Topical antimicrobials included silver sulfadiazine, silver sulfadiazine and enrofloxacin, miconazole, gentamicin and dexamethasone in tris-EDTA, aluminum acetate, amikacin in tris-EDTA, and DMSO and fluocinolone. Eighty-two percent (36) of the dogs resolved in 117 ± 86.7 (30 to 360) days. All were given instructions for prophylactic and maintenance treatment at the time of discharge including ear cleansers, ear cleansers plus aluminum acetate, ear cleansers plus silver sulfadiazine in aluminum acetate, ear cleansers plus silver sulfadiazine and enrofloxacin, or ear cleansers plus miconazole. Seven of 36 (19%) relapsed within 3 to 15 months and were again treated until resolution and returned to a maintenance program.
References


