Pseudomonas Otitis: Controversies & Clinical Approach

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There are no clinically proven protocols for the management of Pseudomonas otitis in the dog, much less the cat. Based on a meta-analysis of **10 trials, 162 patients and 13 different pharmacological interventions** the following was concluded:

"Based on the accepted criteria for quality of evidence, there is insufficient evidence for or against recommending the use of any of these treatments.

Most, if not all, of therapeutic decisions in this condition are based on inadequate published data, personal experience and anecdote, rather than on evidence-based medicine."

Evidence-based veterinary dermatology: a systematic review of interventions for treatment of P*seudomonas* otitis in dogs
Nuttall T and Cole LK: Veterinary Dermatology 18, 69–77, 2007

To deal with Pseudomonas we must make decisions based on the know biology of the organism and our understanding of otic pathophysiology and pharmacology.

Clinical biology

- Over 140 species of *Pseudomonas* have been described and most are saprophytic.
- Specific diseases include glanders (*P. mallei*) and melioidosis (*P. pseudomallei*).
- *Pseudomonas aeruginosa* is an opportunistic pathogen with a predilection for growth in moist environments and is found in soil, vegetation and in faeces.
- Motile Gram –ve aerobic rods that are and can proliferate in an anaerobic environment.
- Very simple nutritional requirements. May grow in almost distilled water, soap and motor fuels. In jet fuel, Pseudomonas toxins corode metal (hydroccarbon-utilizing microorgorganism "HUM bug).

Pathogenic mechanisms

- Rarely infects "normal" tissue, yet there is hardly any tissue that it cannot infect if the tissue defenses are compromised.

- Vast array of exotoxins including toxin A which impairs protein synthesis, causing cell death (similar to Diphtheria toxin)
- Some strains produce a polysaccharide slime layer that:
    - Protects from host immune system
    - Additional barrier to antiseptics and antibiotics
    - Enhances adhesion to fomites/otoscopes
- Multiple antibiotic resistance principally by efflux pumps
- Largest and most complex bacterial genome sequenced. Permits coding for resistance and adaptation.
- Resistance by rapid mutation
- Transferred horizontally via multi-resistance plasmids (conjugation)

Otoscope disinfection

X Wiping and water washing

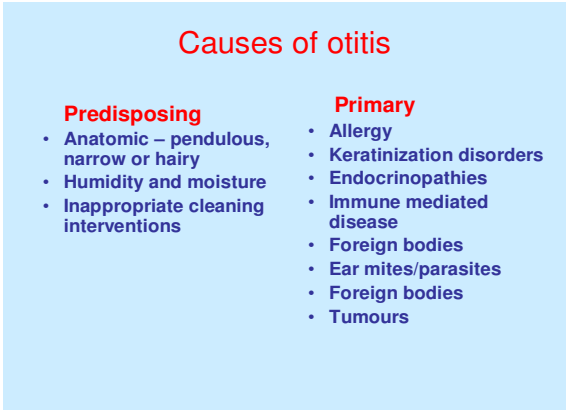
X Wiping with 70% alcohol

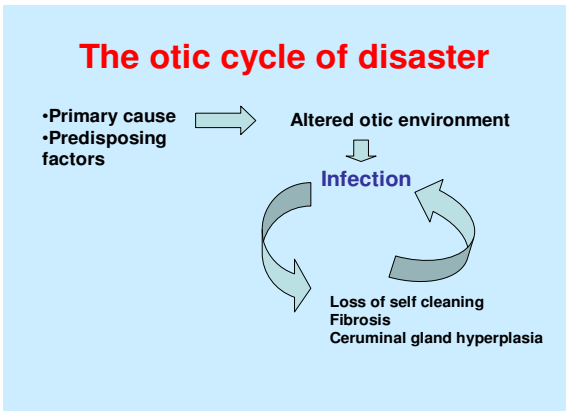
✓ Soaking in 2% chlorhexidine

Newton HM et al: Evaluation of otoscope cone cleaning and disinfection procedures commonly used in veterinary medical practices: a pilot study.
Vet Dermatol. 2006 Apr;17(2):147-50.

All cases of otitis have a primary cause

Just because the primary cause is not obvious, it does not mean there is not one. **The most common primary cause of canine otitis is allergy.** Atopic dermatitis and dietary allergy may manifest as otitis externa alone. If the ear canal has been damaged, the normal cleaning mechanism of ceruminal trapping and sequential exfoliation will not occur.





Predisposing factors to Pseudomonas otitis

- Selection pressure due to repeated courses of antimicrobials
- Moisture, especially the use of saline as an ear cleaner

- Off label weak antiseptics

Clinical findings of Pseudomonas otitis

- Often history of chronicity and of failed, repeated or multiple therapies
- Pain and irritation
- Malodorous purulent exudate
- Ulceration and severe inflammation
- Otitis media

Caution: None of these clinical signs are SPECIFIC for Pseudomonas

Otitis Media

- May be present despite an apparently intact tympanic membrane
- Manifest as:
  - "Head tilting" pain
  - Neurological signs
    - Horner's syndrome
    - Facial nerve deficits
    - Vestibular signs (otitis interna)
    - "Parasympatrhetic" nose or KCS

If in doubt, assume otitis media to be present, Especially if tympanic membrane appears abnormal.

Diagnosis

Cytology

- Neutrophils and rods which may be both extracellular and within neutrophils
- Rods are a feature of Pseudomonas, other Gram –ve bacteria, diphtheroids and anaerobes
- Cytology has only "fair" sensitivity (1/3 organisms cultured not identified by cytology) but good specificity (high% organisms seen are grown)

Culture

- Major Australian laboratories use the CDS protocol (Calibrated Dichotomous Sensitivity). Sensitivity zone size generally >6mm. Reports only "S" or "R". CDS disc concentrations designed to be conservative. May under-report marginal sensitivities. Variation possible without good laboratory technique
- Variation between results for minimum inhibitory concentration (MIC) and disk diffusion. **MIC testing not readily available from Australian veterinary labs**. The MIC is that level of antibiotic that inhibits growth of a standard inoculum of the bacterium in liquid medium. E-test for enrofloxacin available by request.
- Surrogate disks are often used. Ciprofloxacin or moxifloxacin commonly used surrogate disks for enrofloxacin. Multiple studies have demonstrated non-equivalence.

- What do cultures mean with respect to topical therapy? MIC's are expressed in µgm/ml and topical therapy is in mg/ml.

The four pillars of treatment: A sample approach

- Cleaning under anaesthetic
- Corticosteroids
- Triz-EDTA
- Antibiotics

1. Cleaning under anaesthetic

Aims

- Reduction of bacterial load
- Eliminating nidus and substrates for bacteria
- Remove inflammatory toxins
- Remove organic matter that inhibits antibiotics (polymyxin and aminoglycosides)

Use only warm saline only until tympanic membrane seen to be intact. Be prepared to repeat the procedure. Frequency depends on period canal remains exudate free

2. Corticosteroids

- In topical medications
- Systemically 1mg/kg for 7-10 days followed by every second day for a similar period
- Intra-mural injections for reduce polyp-like thickenings

Objectives:

- Reduce pain and inflammation
- Reduce secretions and ceruminal hyperplasia
- Inhibit and address canal thickening

3. Triz EDTA

4. EDTA binds Ca++ ions and increased permeability to antibiotics and has a bactericidal effect
5. Triz buffer provides alkaline pH. Optimizes aminoglycosides and fluoroquinolones
6. Lower end of ototoxic spectrum
7. Vehicle for off label antibiotics, corticosteroids and 0.15% chlorhexidine
8. Instilled 10 mins before other medication

4. Antibiotics

Topical antibiotics

- No evidence if 1x or 2x day optimal. No evidence if 1x or 2x day optimal. Aminoglycosides and fluoroquinolones concentration dependent

- Evidence of addition or synergy between enrofloxacin and silver sulfadiazine.

Criteria for choice of a topical antibiotic

- Culture: choose (S) over (R)
- Known sensitivity patterns if (R)
- Registered over unregistered
- Choose safer over less safe if other criteria equal
- Be prepared to change

Ototoxicity

- Nothing other than saline is safe
- Incidence of ototoxicity unknown but MUCH less than the clinical use of ototoxic agents with ruptured tympanic membranes. A study on dogs with experimentally ruptured tympanic membranes failed to demonstrate toxicity with 21 days of 3% gentamicin drops used twice daily.
- Effect of flush under pressure may be different to simple instillation of the same drug, particularly with respect to access to the inner ear.
- Vehicles may be ototoxic (propylene glycol)

Systemic antibiotics in Pseudomonas otitis

- Lack of studies to prove or disprove value
- Need to understand pharmacology and kinetics of agents so as to **deliver effective dose to the target tissues of the ear.**

General Indications

- Otitis media
- Refractory ulceration
- Impenetrable thickening
- Inability to medicate
- Complementing same topical medication??
- Use as per deep pyoderma – 4-12 weeks or 2-3 weeks beyond clinical cure

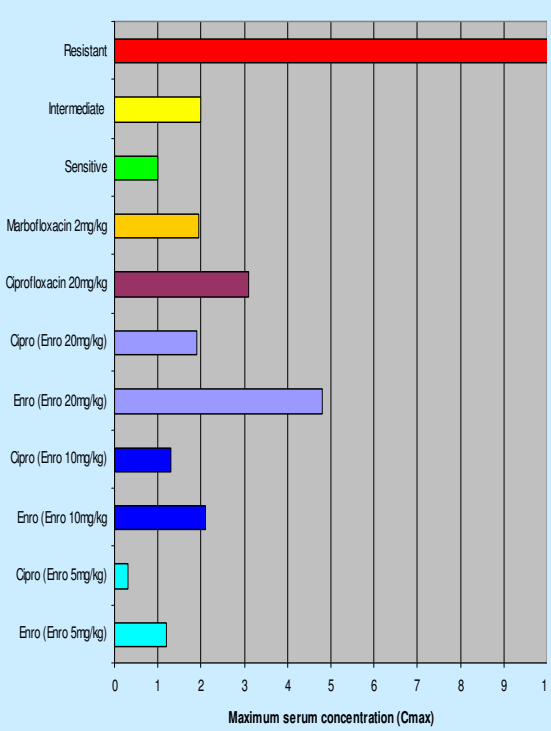
Indicative sensitivity data of otic Pseudomonas stains by various methods and from various countries

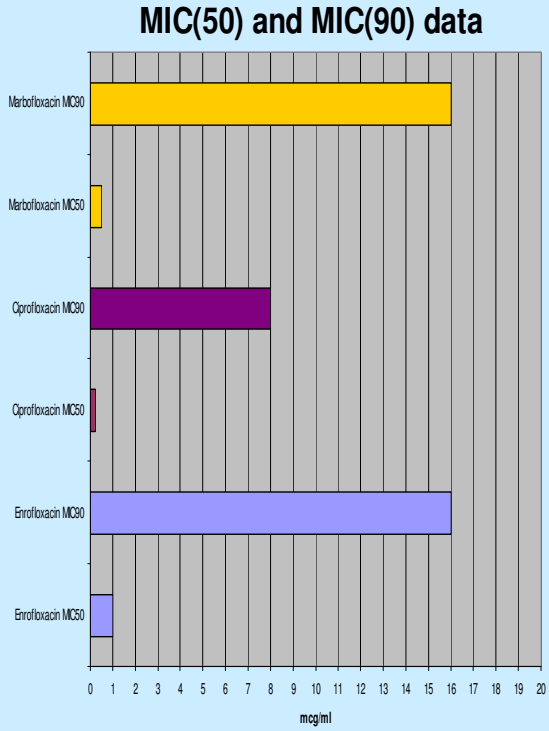
Enrofloxacin	47	69	–	52	63	–
Enro/Silver SD	–	–	–	–	82	–
Ciprofloxacin	77	84	–	–	–	–
Marbofloxacin	67	73	–	92	–	–
Gentamycin	–	93	85	86	–	75(1)
Amikacin	–	97	–	–	–	–
Tobramycin	–	–	–	100	–	–
Polymyxin-B	–	–	100	–	–	43
Ticarcillin	–	–	–	75	–	–
Ceftazidime	–	93	–	92	–	–
Neomycin	–	–	–	–	–	53

Fluoroquinalone issues

- Non- equivalence of fluoroquinolones. In the case of Pseudomonas, marbofloxacin <> enrofloxacin <> ciprofloxacin <> orbifloxacin with respect to sensitivities, absorbtion and peak plasma concentration. Approximately 40% of enrofloxacin is metabolized to ciprofloxacin.
- Concentration dependent rather than time dependent. Optimal effects when maximum concentration at the site of infection (Cmax) exceeds MIC (minimum inhibitory concentration) by a significant multiple.
- MPC (mutant prevention concentration) may be 10-20x the MIC and can't be determined from MIC data
- Concentrates in leucocytes and higher levels in inflamed tissue. There may be significantly higher levels of drug at the site of infection as compared to plasma concentration.
- Post antibiotic effect: "Wounded bacteria". The microbes continue to be impaired for a period after the concentration of the drug has dropped below the MIC.
- Silver sulfadiazine may have additive or synergistic effects

Maximum serum concentrations (Cmax) and MIC50/90's





Most data USP fluoroquinolones monograph 2007

In the case of systemic dosing with fluoroquinolones at standard dose rates, peak plasma levels are similar to the MIC of sensitive strains or at best those with intermediate resistance. The peak levels are of the same order as that required to inhibit 50% of strains (MIC50) but vastly below MIC90 levels.

Maintenance and follow-up is essential

- Identify and treat primary cause. Without addressing the primary cause, the conditions that permitted colonization by bacteria will persist and re-infection is almost certain.
- Cleaning protocol. If the ear canal has been damaged, the normal cleaning mechanism of ceruminal trapping and sequential exfoliation will not occur. An anti-Pseudomonas cleaning protocol is often effective in preventing re-colonization. e.g. 2% acetic acid
  - Anti-Pseudomonas effect not pH related
  - Well tolerated
  - May have synergy with boric acid
- Follow up. Monitor progress by otoscopic examination and cytology regularly.

Reasons for failure

- **Not cleaning appropriately**
- **Not treating long enough**
- **Not resolving otitis media**
- **Proliferate and end-stage ears**
- **Poor owner compliance**
- **Inappropriate antibiotics**
- **Failure to address primary cause**
- **Failure to maintain**

Surgical treatment

Lateral ear resection

- Allows access to inflammatory polyps or tumours
- Almost certain continued medical management will be required

Total ear ablation with lateral bulla osteotomy.

Indications:

- Failure of appropriate medical management
- Intractable otitis media
- End stage canal changes
- Tumours
- Inability or unwillingness to medicate

Future developments

- Use of ear wicks, especially in stenotic/scarred ears
- Monosaccharides to inhibit attachment of bacteria to tissue by competing for attachment receptors
- Placebo controlled prospective clinical trials

References available by request