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# The Effectiveness and Safety of Antibiotic Treatment in Healing Tympanic Membrane Perforation in Aboriginal Children

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# The Effectiveness and Safety of Antibiotic Treatment in Healing Tympanic Membrane Perforation in Aboriginal Children

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## Abstract

### Objective

The objective of this systematic review is to determine whether or not antibiotic treatment is safe and effective in healing tympanic membrane (TM) perforation in Aboriginal children diagnosed with chronic suppurative otitis media and otitis media with effusion less than 16 years of age.

### Study Design

The author conducted a review of three studies published in English in peer-review journals. One of these studies was published in 2003 and the other two in 2008.

### Data Sources

All three studies were conducted as either double-blinded or assessor-blinded randomized controlled trials. The author found the articles through the Ovid and Cochrane databases.

### Outcomes Measured

The outcomes measured for each of the three trials was the TM perforation size or healing at the end of the study treatment with either topical framycetin (0.5%), gramicidin, and dexamethasone (FGD), topical ciprofloxacin or long-term systemic amoxicillin.

### Results

One study, which compared topical FGD to topical ciprofloxacin and assessed TM perforation at the end of therapy noted 23% of patients treated with FGD and 26% of patients treated with ciprofloxacin as having a one or two step decrement in TM perforation at the end of treatment. The second study comparing topical FGD to topical ciprofloxacin noted 100% of patients treated with FGD and 98% of patients treated with ciprofloxacin having failure to heal TM perforation at the end of therapy. The study looking at long-term systemic amoxicillin versus placebo for TM perforation healing noted 27% of placebo patients and 12% of amoxicillin patients with remaining TM perforation at the end of the trial.

### Conclusions

In this systematic review neither topical FGD nor topical ciprofloxacin significantly changed TM perforation size after treatment. Significant results, however, are noted in TM perforation prevention with use of long-term systemic amoxicillin.



### Key Words

Antibiotic treatment, amoxicillin, framycetin-gramicidin-dexamethasone (FGD), ciprofloxacin, otitis media, Aboriginal children

**Introduction**

Otitis media (OM) is an infection seen in patients of all ages, but most commonly seen in the pediatric population. Current treatment for otitis media with effusion (OME) and chronic suppurative otitis (CSOM) may not be effective enough to prevent complications in high-risk populations, such as those of low socioeconomic status and those who are medically underserved, underinsured or uninsured. This paper evaluates three clinical randomized controlled trials on the prevention and treatment of tympanic membrane perforation. Two trials compare the use of topical ciprofloxacin and a topical aminoglycoside containing framycetin (0.5%), gramicidin, and dexamethasone (FGD) in Aboriginal children with CSOM while the third looks at the long-term use of systemic amoxicillin in Aboriginal children with OME.

The topic of effective treatment for otitis media is important to Physician Assistants, especially to those working in the specialties of family medicine, primary care or pediatrics. Acute otitis media is the most common reason that children see a clinician with 30 million pediatric physician visits each year. Clinicians with exposure to the pediatric population must be knowledgeable in the treatment of OM[6]. In addition, those Physician Assistants working with the "high-risk" populations described above must be aware that certain complications such as CSOM or progression of AOM to tympanic membrane (TM) perforation are more common in these populations. Additional risk factors of OM include children in daycare, those with multiple siblings, exposure to cigarette smoke in the home, Down's syndrome, pacifier use or formula feeding[6]. In 1995 it was estimated that 2.95 billion dollars were spent on pediatric OM office visits indicating the great deal of resources used for diagnosis of OM and the importance of effective treatment[8].

Otitis media in an infection of the middle ear associated with effusion or otorrhea and can progress to a chronic suppurative state if left untreated or if treated ineffectively. This infection develops from respiratory tract inflammation leading to eustachian tube dysfunction and development of transudate in the middle ear. Colonization and subsequent infection of the transudate with viral or bacterial pathogens in the middle ear lead to acute or chronic otitis media. Untreated acute OM can progress to TM perforation, CSOM and childhood hearing loss, which have adverse effects on child development[7]. This review is primarily concerned with the antibiotic effect in healing TM perforations because of the detrimental progression to childhood hearing loss and developmental delay.

Currently the first line treatment for OM is systemic amoxicillin, 90 mg/kg/d up to 4 g/d for five days in children older than two years and for 10 days in those less than two years old. OM refractory to amoxicillin should be treated with systemic augmentin ES-600, 90 mg/kg/d. OM with effusion persisting for more than four months is treated with ventilating tubes[3]. The treatment for CSOM in the US is a topical fluoroquinolone while in Australia the preferred treatment for CSOM is topical FGD, which is more effective than systemic antibiotic in treating otorrhea seen in CSOM[2]. The dilemma and reason for this systematic review is two-fold. One, the first-line therapy for acute OM is amoxicillin for five to 10 days but no studies have shown whether long-term antibiotic treatment is safe and effective in high-risk populations with persistent OM[4]. Second, the current first-line treatment for CSOM in Australia is topical FGD despite the known ototoxicity of aminoglycosides. Topical ciprofloxacin has potential as a treatment alternative to FGD and some studies show it is more effective in improving the otorrhea of CSOM. The safety and efficacy of topical ciprofloxacin in treatment of CSOM in Aboriginal children is unknown[2,5].

**Objective**

The objective of this systematic review is to determine whether or not antibiotic treatment is safe and effective in healing tympanic membrane (TM) perforation in Aboriginal children diagnosed with CSOM and OME less than 16 years of age.

**Methods**

A strict criterion was used to select the participants of the study. The population included Aboriginal children less than 16 years of age with OME and CSOM. Two of the studies included children from Aboriginal communities of northern Australia while the third study included three remote Aboriginal communities in various regions of Australia[2,4,5]. The interventions being studied are topical FGD, topical ciprofloxacin and long-term systemic amoxicillin for treatment of TM perforation. All three studies were randomized controlled trials (RCT). In two of the RCTs the treatment groups received ciprofloxacin and the placebo group received FGD. In the third RCT the treatment group received systemic amoxicillin and the placebo group received no treatment. The outcome measured was the size and healing of TM perforation at the end of treatment, which qualifies as disease-oriented evidence (DOE) not patient oriented evidence that matters (POEM)[2,4,5]. Had the investigators added a preventative element to their study such as limiting OM risk factors such as smoking in the home or advising against activities that might worsen TM perforation such as swimming then the outcome would have been one that the study participants were actively involved in changing thus making it a POEM.

The author of this review conducted the data searches on the Ovid and Cochrane database using the keywords “otitis media”, “aboriginal children” and “antibiotic treatment” from 1996 to the present. All three articles chosen for the systematic review were written in English and were published in peer-review journal articles. Articles included in the review were any RCT that

studied the use of antibiotic therapy in Aboriginal children with some form of OM less than 16 years of age. Articles excluded from the study were those that were two variations of the same study by the same author. The statistics reported in the three studies were CER (control event rate), EER (experimental event rate), relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT) and the confidence interval (CI). A *p-value* was reported for the data specifically regarding TM perforation size or healing for only one of the three studies [2,4,5]. Table one details the specific studies reviewed including the type of study, the number and age of patients, inclusion and exclusion criteria, and withdrawals and interventions.

Table 1- Demographics and characteristics of included studies

| Study | Type | # Pts | Age (yrs) | Inclusion criteria | Exclusion criteria | W/D | Interventions |
|---|---|---|---|---|---|---|---|
| Couzos, S., Lea, T., Mueller, R., Murray, R. et al. (2003) | Double-blind, randomized controlled trial | 147 | 1-14 years | Aboriginal children; <15 years; At least 2 weeks of otorrhea; TM perforation | Febrile illness; abx use in past 2 weeks; ototopical med allergy; fluoroquinolone allergy; need for renal dialysis; recent ear surgery; in-situ ear tube; hearing loss; obstructed middle ear; pregnancy; unlikely to be resident at end of study | 36 | Topical ciprofloxacin vs. topical FGD, 5 drops 2x/day to bilateral ears x 9 days |
| Leach, A. J., Morris, P. S., Mathews, J. D. et al. (2008). | Double-blind randomized controlled trial | 103 | < 12 mths | Aboriginal infant; unilateral or bilateral OM with effusion | Prematurity (<34 wks); chronic infection requiring prophylactic therapy; craniofacial abnormality; immune deficiency syndrome | 9 | Amoxicillin 50 mg/kg/day BID vs. placebo x 24 weeks to bilateral ears |
| Leach, A., Wood, Y., Gadil, E. et al. (2008) | Randomized assessor-blinded controlled trial | 97 | 1-16 years | Aboriginal children; chronic perforation | Abx allergy; pregnancy; breast-feeding; tympanoplasty; cholesteatoma; severe medical illness | 8 | Topical Ciprofloxacin vs. topical FGD, 4 drops 2x/day to bilateral ears |

**Outcomes measured**

In the Leach, Wood et al. study, the outcome measured was whether or not there was any remaining TM perforation at end of therapy. TM perforations were measured through otoscopy, video-otoscopy and drawings of the TM. The proportion of the TM perforation size to the TM

surface area was determined. Two separate clinical assessors analyzed the video otosocopy and the results were compiled. A third assessor resolved any differences in clinical assessment.

Couzos, Lea et al. looked for a one or two-step decrement in size of TM perforation at the end of treatment. The authors did not give information regarding how they determined a "one" versus "two-step" decrement in TM perforation size. Video otoscopy was used to assess the size of the TM perforation as a proportion of the TM surface area. Aboriginal health workers participating in the study and two otolaryngologists conducted the assessment of TM perforation.

Leach, Morris et al. studied whether or not there was any remaining TM perforation at the end of therapy. Clinical records on the study participants were used to assess baseline characteristics and pre-enrollment ear disease. The study participants were examined every two weeks from the time of enrollment to the time of randomization. Participants were also assessed monthly during the six month intervention period or until success was documented. An Australian expert trained physicians and nurses to use video pneumatic otoscopy and tympanometry to assess ear status, including TM perforation during and after the intervention.

**Results**

All three studies were conducted in the primary care outpatient setting with results being presented as dichotomous data. The results of the studies by Leach, Wood et al. and Leach, Morris et al. were examined using the "intention to treat analysis". Patients enrolled in these two studies were included in the analysis even if they withdrew from the study or were lost to follow-up. The most recent data on those patients who withdrew from the study or were lost to follow-up was analyzed or the patient was counted as a treatment failure. In the Couzos, Lea et al. study, the children who were lost to follow-up were not included in the final data analysis so no "intention to treat" analysis was performed.

Two of the three studies included in this review were randomized, double-blind controlled trials while one was a randomized, assessor-blinded controlled trial. In two of the studies, the treatment groups received ciprofloxacin while the placebo received FGD. In the third study the treatment group received long-term systemic amoxicillin and the placebo group received no treatment. The Couzos, Lea et al. trial included children from one to 14 years with two weeks of otorrhea and TM perforation, the Leach, Morris et al. study included children less than 12 months old with bilateral OME and the Leach, Wood et al. study included children one to 16 years old with chronic TM perforation.

Not all patients that were enrolled in each study completed the study. In the Leach, Morris et al. study, 103 infants were randomized with two in the amoxicillin group and seven in the placebo group discontinuing therapy. One infant in the amoxicillin and two in the placebo group were withdrawn due to CSOM, while one infant in the amoxicillin group and three in the placebo group were withdrawn by the parent for unspecified reasons. No patients in the amoxicillin group and two patients in the placebo group were lost to follow-up. In the Couzos, Lea et al. study 147 patients were randomly allocated while 36 patients did not complete the study and were not included in the study analysis due to lack of sufficient data. Out of the 36 patients who did not complete the study, 18 were lost to follow-up, eight had incomplete follow-up, nine withdrew for unknown reasons and one withdrew because the patient's otorrhea improved. In the Leach, Wood et al. study, 50 patients in the treatment group and 47 in the placebo group were randomized with five in the treatment group and three in the placebo group that did not complete the study for unspecified reasons.

The results of the Leach, Morris et al. study were based on treatment of the amoxicillin group for 5.7 months and the placebo group for 5.2 months. The outcome measured was whether

there was any residual TM perforation present at the end of the therapy (see table 2 below). 12% of those patients in the amoxicillin group and 27% of patients in the placebo group showed TM perforations at the end of therapy. The RBI was –58%, the ABI was –16% and the NNT was –7 which signifies that for every seven patients treated with amoxicillin, there was one fewer patient with a perforated TM at the end of therapy than in the placebo group. The 95% confidence interval was 16 [-31, -1] (see table 3 below).

In the Couzos, Lea et al. study the treatment was for nine days and the clinical outcome measured was a decrement (either one or two-step) in TM perforation size at the end of the study (table 2). In the topical ciprofloxacin (experimental) group 26% of participants had a one or two-step decrement in TM perforation size as opposed to 23% in the topical FGD (control) group. The RBI was 13%, the ABI was 3% and the NNT was 32 meaning that for every 32 patients treated with topical ciprofloxacin, there is one more patient with a decrease in the size in the TM perforation than in the topical FGD group. No confidence interval was reported (table 3) but the reported *p-value* was 0.21 meaning the data is not statistically significant.

The Leach, Wood et al. trial studied the experimental and control treatments for six to eight weeks with the measured clinical outcome as any remaining TM perforation at the end of therapy (table 2). In the topical ciprofloxacin (experimental) study group, 98% had TM perforation remaining at the end of therapy as opposed to 100% in the topical FGD (control) group. The RBI was –2% the ABI was –2% and the NNT was -50 signifying that for every 50 patients treated with topical ciprofloxacin, one fewer patient had failure of the TM perforation to heal after treatment than those patients treated with FGD. The 95% confidence interval was reported as 2 [-6 to 2] (table 3).

Table 2: Details of study samples, treatment duration and clinical outcomes measured

| Study | No. of pts in data analysis | Mean treatment duration | Outcome measured |
|---|---|---|---|
| Leach, A. J., Morris, P. S. et al. (2008). | 103 | Amoxicillin 5.7 months<br>Placebo 5.2 months | Any remaining TM perforation at end of therapy |
| Couzos, S., T, Lea, T. et al. (2003) | 111 | 9 days | One or two step decrement in TM perforation size |
| Leach, A., Wood, Y. et. al. (2008) | 97 | 6-8 weeks | Failure to heal perforation |

Table 3: Tympanic membrane perforation at end of treatment period

| Study | CER | EER | RBI | ABI | NNT | CI or p-value |
|---|---|---|---|---|---|---|
| Leach, A. J., Morris, P. S. et al. (2008) | Placebo 27% | Amox 12% | -58% | -16% | -7 | CI: 16 [-31, -1]<br>*P-value:* not reported |
| Couzos, S., Lea, T. et al. (2003) | FGD 23% | Cipro 26% | 13% | 3% | 32 | CI: not reported<br>*P-value*: 0.21 |
| Leach, A., Wood, Y. et. al. (2008) | FGD 100% | Cipro 98% | -2% | -2% | -50 | CI: 2 [-6 to 2]<br>*P-value*: not reported |

The Leach, Morris et al. trial performed no discussion of patient compliance or treatment adherence. The study does report that none of its participants were withdrawn due to "direct" adverse reactions of the given medication though one child in the amoxicillin group and two in the placebo group for withdrawn for continued CSOM despite treatment (see table 4 below).

No issues with patient compliance of ototopical treatment whether experimental or control were detailed in the Couzos, Lea et al. study. Child guardians of the study participants performed half of the study treatments while study workers performed the other half of the treatments possibly reducing the chance of treatment noncompliance that may have been seen had the child guardian been the sole treatment administrator. The study reports 21 "minor" adverse reactions of the treatment stating 14 children noticed a bitter taste when given the ototopical drops, five complained or ear pain and three of dizziness (table 4).

In the study discussion, Leach, Wood et al. make reference to the idea that there is room for improvement in treatment adherence in the studied population but does not give specific statistical data regarding adherence difficulties found in the study. Also, the report states that out

of the twice daily ototopical treatments, study health workers supervised the morning dose and family members administered the evening dose. It is possible that morning supervision of treatment is likely to have increased overall treatment compliance. The study also mentions that although ototoxicity was not directly measured in the study, there was no difference in hearing loss between the FGD and ciprofloxacin groups at the end of the study period (table 4).

Table 4: Adverse outcomes of studies

| Study | Ototoxicity | Ear pain | Dizziness | Bitter taste | Unresolved CSOM |
|---|---|---|---|---|---|
| Couzos, S., Lea, T. et al. (2003) | None | 5% | 3% | 14% | No mention |
| Leach, A. J., Morris, P. S. et al. (2008) | No mention | No mention | No mention | No mention | 3% |
| Leach, A., Wood, Y. et al. (2008) | None | No mention | No mention | No mention | No mention |

**Discussion**

The studies by Couzos, Lea et al. and Leach, Wood et al. demonstrate no significant change in TM perforation size before or after the study period with either topical FGD or ciprofloxacin treatment. The confidence interval for the Leach, Wood et al. study is narrow meaning the authors can be confident that the results of their data are valid. Although no confidence interval was reported for the study by Couzos, Lea et al., the *p-value* for the measured outcome was 0.21 meaning that the results are not statistically significant and more likely due to chance. The study by Leach, Morris et al. notes significant prevention in TM perforation with use of long-term amoxicillin. The confidence interval for the Leach, Morris et al. study is moderately wide signifying more studies should be done before definitively stating the effectiveness of amoxicillin in TM perforation prevention.

One of the potential drawbacks of the aminoglycoside containing ototopical FGD is that it is known to be ototoxic. The studies with FGD and ciprofloxacin treatment state there were no participants with ototoxicity as a result of FGD use at the follow-up period, which was several

months after the study end. Thus, the risk of ototoxicity with aminoglycoside use may be less common than previously thought so a longer follow-up period regarding ototoxicity is warranted.

Amoxicillin is one of the most commonly used pediatric drugs, is generally safe and is available in an oral form. A clinician must be aware of the potential amoxicillin side effects especially when using the drug long-term as suggested in this review. Examples of some side effects are stomach upset, vomiting, diarrhea, rash, tooth discoloration, hepatic dysfunction and hematologic dysfunction such as hemolytic anemia. Amoxicillin must be dose adjusted in pediatric renal patients. It is contraindicated in patients taking other drugs such as probenecid or methotrexate. It is considered to be in pregnancy category B and is found in breast milk.

The rural location of the studies and lower socioeconomic status of the Aboriginal population in Australia is a limitation to the three studies. As stated in several of the studies, adherence to specific medication regimens for the amount of time specified may have been difficult in this particular population. Consistency and strict adherence to the medication regimen can be difficult especially in families with several child caretakers, caretakers that work or in lower income families prone to psychosocial issues affecting proper medication administration.

Another potential limitation of the systematic review as a whole was the variation between the different studies in the initial TM perforation size prior to treatment. The study by Couzos, Lea et al. states that the study participants had varying sizes of TM perforations at the beginning of the study trial though there was no association between the clinical cure and the initial size of the TM perforation. In the report by Leach, Morris et al. the majority of study participants had only OME so the lack of initial TM perforation had no effect on TM perforation healing. In the study by Leach, Wood et al. the TM perforation at the end of treatment was measured as a percentage of the initial TM perforation minimizing the chance that initial

perforation size could have affected the study outcome. As described above there were a variety of initial TM states between the three studies even though the initial condition of the TM had no effect on the ending condition. Future systematic reviews on antibiotic therapy for TM perforation should have more consistency in the initial state of the TM so as to minimize unknown outside factors potentially affecting study data.

**Conclusion**

A thorough review of the articles by Leach, Morris et al. (2008), Couzos, Lea et al. (2003) and Leach, Wood et al. (2008) demonstrates that neither ototopical FGD nor ciprofloxacin are effective in healing TM perforation though they were found to be safe. Systemic amoxicillin does appear to be safe and effective when compared to placebo in preventing TM perforation. It must be noted that the conclusion of amoxicillin's effectiveness is based upon a review of one research article with a moderately wide confidence interval. Another systematic review containing two or more studies of amoxicillin in treating TM perforation is more ideal in confirming or disproving its effectiveness.

The data obtained from this systematic review should be used as a guideline for future studies looking at treatment of the various forms of OM seen in high-risk US children such as those living in urban settings or low-income communities. As of December 2010, no systematic reviews, to the knowledge of the author, have been performed in the US looking specifically at treatment of OME or CSOM in high-risk or lower income children. Studies looking at treatment of AOM have been conducted in higher income countries and a systematic review looking at long-term treatment in prevention of acute and chronic suppurative otitis media has been performed in higher-risk populations from various countries, but none specifically in the US alone. The data demonstrated in this systematic review is applicable to high-risk populations in

the US though there may be genetic, cultural and other differences between the Aboriginal population and high-risk populations in the US warranting US specific studies.

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