Acute otitis media in children with tympanostomy tubes

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ABSTRACT

OBJECTIVE To review evidence regarding antibiotic treatment of acute otitis media in children with tympanostomy tubes and to discuss antibiotic resistance and ototoxicity.

QUALITY OF EVIDENCE MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials were searched for relevant articles. Articles providing level I evidence (randomized controlled trials) for treatment were used. Key words used in the search included *otitis media* (MeSH), *middle ear ventilation* (MeSH), *tympanostomy tubes,* and *otorrhea.*

MAIN MESSAGE Tympanostomy tube insertion is a common procedure; acute otitis media is a frequent sequela. Treatment options include systemic or topical antibiotics with or without corticosteroids. The development of bacterial resistance to antibiotics and ototoxicity related to treatment are important considerations. There have been well-conducted randomized controlled trials of topical versus systemic antibiotic agents. Combined with proper ear cleaning and tragal pumping, topical fluoroquinolone agents offer the most effective treatment.

CONCLUSION Current evidence suggests that a topical fluoroquinolone, with or without a corticosteroid, is the treatment of choice for acute otitis media with tympanostomy tubes.

RÉSUMÉ

OBJECTIF Revoir les données concernant le traitement antibiotique de l'otite moyenne aiguë chez l'enfant porteur de tubes de paracenthèse et discuter de résistance aux antibiotiques et d'ototoxicité.

QUALITÉ DES PREUVES Les articles pertinents ont été relevés dans MEDLINE, EMBASE, la Cochrane Database of Systematic Reviews et dans le Cochrane Central Register of Controlled Trials, à l'aide des mots clés *otitis media* (MeSH), *middle ear ventilation* (MeSH), *tympanostomy tubes*, et *otorrhea*.

PRINCIPAL MESSAGE L'insertion de tubes tympaniques est une technique courante qui peut souvent entraîner une otite moyenne aiguë. Les options de traitement incluent les antibiotiques systémiques ou topiques avec ou sans corticostéroïdes. Le développement de résistance bactérienne aux antibiotiques et l'ototoxicité doivent être pris en considération. Il existe des essais randomisés bien contrôlés comparant les antibiotiques topiques aux systémiques. Combinés à un nettoyage adéquat de l'oreille et à un pompage du tragus, les fluoroquinolones topiques représentent le traitement le plus efficace.

CONCLUSION Les données actuelles suggèrent que les fluoroquinolones topiques associés ou non à un corticostéroïde constituent le traitement de choix de l'otite moyenne aiguë en présence de tubes tympaniques.

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Myringotomy with tympanostomy tube insertion is the most common operation performed on children in Canada.[1] Otorrhea is the most common complication following tube insertion and can occur in up to 17% of intubated ears.[2-5] Most patients experience discomfort and some degree of hearing loss. The most common cause of tympanostomy tube otorrhea is acute otitis media (AOM).[6] Acute otitis media with tympanostomy tubes (AOMT) differs clinically and microbiologically from AOM with an intact tympanic membrane in that AOMT frequently presents with sudden onset of purulent otorrhea rather than earache and fever.[7] Both Gram-negative and Gram-positive bacteria are associated with AOMT, including *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* and *Pseudomonas aeruginosa.* However, *S aureus* and *P aeruginosa* are found more often in tube otorrhea than AOM, because they are commonly found in the external auditory canal and can penetrate the middle ear through the tympanostomy tube.[8,9] Otorrhea might resolve spontaneously or might require antimicrobial treatment.[10] Treatment with either systemic antibiotics or topical ear drops provides improved outcomes, but bacterial resistance and ototoxicity should be considered when selecting therapy.[11]

Family physicians play an important role in treating AOMT given its prevalence in office practice. In this article, we review the evidence regarding antibiotic treatment of AOMT and discuss antibiotic resistance and ototoxicity.

Quality of evidence

We searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials for relevant articles using the key words *otitis media* (MeSH), *middle ear ventilation* (MeSH), *acute otitis media, tympanostomy tubes, grommets,* and *otorrhea.* We limited articles to systematic reviews, meta-analyses, randomized controlled trials, and clinical controlled trials, and only included studies with human participants. The search produced 245 results. Reference lists of selected articles were scanned for additional relevant articles. From the results, we selected only randomized controlled trials (level I evidence) to review treatment of AOMT. In total, we identified 7 randomized controlled trials. One trial was excluded because the treatment studied is not available in North America.

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Treatment

Several studies of AOMT have examined treatment with systemic or topical antibiotics. The available randomized controlled trials on the treatment of AOMT are summarized here.

Systemic antibiotic (amoxicillin-clavulanate) versus placebo. In a randomized, double-blind, placebo-controlled trial of 66 children aged 6 to 72 months, researchers examined antimicrobial treatment of AOMT.[12] Patients were treated with daily suction and amoxicillin-clavulanate (45 mg/kg daily) or placebo. Outcome measures included duration of otorrhea and bacterial growth. Those in the intervention group experienced a significantly shorter duration of otorrhea (3 vs 8 days, $P=.002$) and less middle ear bacterial growth compared with those in the placebo group. Mild adverse events, mainly gastrointestinal, affected 8 patients in the intervention group and 1 who received placebo. Two children taking amoxicillin-clavulanate were withdrawn from the study (1 owing to tube extrusion and the other because of vomiting); 5 children were withdrawn from the placebo group (1 owing to contralateral AOM with perforation, 1 because of eczema, 1 because of tube granuloma, and 2 because of tube extrusion).

Systemic corticosteroid (with systemic antibiotic) versus placebo (with systemic antibiotic). A randomized, double-blind, placebo-controlled study was conducted assessing 3-day treatment of AOMT with prednisolone (2 mg/kg daily) (n=23) or placebo (n=27). All participants received amoxicillin (40 mg/kg daily) and clavulanate (10 mg/kg daily) for 7 days.[13] The study period was 7 days, and suction was completed at daily follow-up visits. Participants were children aged 6 months to 12 years with tympanostomy tubes and otorrhea during the 48 hours before examination. In per-protocol analysis, the mean duration of otorrhea was 1 day in the intervention group compared with 3 days in the placebo group ($P<.001$). In intention-to-treat analysis, the median duration of otorrhea was 1 day in the intervention group and 4 days in the placebo group ($P<.001$). Diarrhea was experienced by 2 children in the placebo group. Notably, 20 of 70 enrolled patients were excluded from analysis owing to noncompliance, tube extrusion

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

and closure of membrane, dropping of the tube into the middle ear, occlusion of the tube, isolation of bacteria resistant to amoxicillin-clavulanate, tube granuloma, tympanostomy tube insertion in the previous 2 weeks, or loss to follow-up.

Systemic antibiotic (amoxicillin-clavulanate) versus topical antibiotic (ofloxacin). Systemic amoxicillin-clavulanate was compared with topical ofloxacin in a multicentre, randomized, parallel-group, evaluator-blind study.[14] Children (N=474) ages 1 to 12 years with tympanostomy tubes and acute purulent otorrhea were randomly allocated to receive ofloxacin otic solution (0.3%) twice daily or amoxicillin-clavulanate oral suspension (40 mg/kg) 3 times daily, for 10 days. The absence of otorrhea and eradication of baseline pathogens were outcome measures. Clinical cure, for evaluable participants, was achieved for 76% of participants who received ofloxacin and for 69% of those treated with amoxicillin-clavulanate; this was not statistically significant. Overall microbiological eradication of baseline pathogens was significantly higher in the ofloxacin group compared with amoxicillin-clavulanate (96% vs 67%, $P<.001$). Treatment-related adverse events were experienced in 6% of patients treated with ofloxacin compared with 31% of patients treated with amoxicillin-clavulanate ($P<.001$). The most commonly reported adverse events included rhinitis, fever, diarrhea, coughing, and upper respiratory tract infection. Efficacy was similar for both treatments, but patients who received systemic treatment experienced more treatment-related adverse events. Almost 40% of those randomized were excluded. In most of these cases, *Pseudomonas* organisms were the sole pathogens, and the researchers cited the resistance of these pathogens to treatment as the reason for excluding most of these participants. Authors of a systematic review of treatments for AOMT did not include this trial given the high exclusion rate.[15]

Another study compared topical ciprofloxacin (0.3%) plus dexamethasone (0.1%), 4 drops twice daily for 7 days, with oral amoxicillin (600 mg) plus clavulanic acid (42.9 mg) every 12 hours for 10 days.[16] This randomized controlled trial was an observer-masked, multicentre study of 80 children, 6 months to 12 years of age, with AOMT less than 3 weeks' duration. The authors found that the ciprofloxacin-dexamethasone treatment resulted in a significant reduction in duration of otorrhea (4 vs 7 days, $P=.0006$) and a significantly improved cure rate (85% vs 59%, $P<.01$). They also found fewer adverse events with the topical treatment.

Topical antibiotic with a steroid versus topical antibiotic alone

Ciprofloxacin-dexamethasone versus ciprofloxacin: Investigators completed a randomized, patient-masked, parallel-group, multicentre trial comparing topical ciprofloxacin (0.3%) plus dexamethasone (0.1%) with ciprofloxacin alone in 201 children aged 6 months to 12 years with AOMT.[8] Investigators were not blind to treatment group because one treatment was a solution and the other was a suspension. Patients who received ciprofloxacin-dexamethasone twice daily for 7 days had a significantly shorter mean time to resolution of otorrhea than those in the ciprofloxacin group (4.22 vs 5.31 days, $P=.004$). Analysis was done after culture-negative patients were excluded. In a separate intent-to-treat reanalysis including culture-negative patients, however, no significant difference in duration of otorrhea was found between groups at day 8 (odds ratio 0.57, 95% confidence interval 0.32-1.03).[15] Furthermore, no significant difference in cessation of otorrhea was found between groups at 7 days posttreatment (day 14), and the difference in microbiological eradication between groups was not significant on day 14 (90.7% vs 79.7%, $P=.066$). Each treatment was well tolerated and no serious therapy-related events occurred. Although investigators concluded that the addition of dexamethasone to the topical antibiotic resulted in faster resolution of otorrhea, the difference was not clinically significant.

Ciprofloxacin-dexamethasone versus ofloxacin: Ciprofloxacin-dexamethasone has been compared with ofloxacin for the treatment of AOMT in a multicentre, randomized, observer-masked, parallel-group trial. The sample consisted of 599 children between the ages of 6 months and 12 years with AOMT for 3 weeks or less.[17] Patients received ciprofloxacin-dexamethasone, 4 drops twice daily for 7 days, or ofloxacin, 5 drops twice daily for 10 days. Clinical cure, defined as absence of otorrhea, was assessed at day 18. Patients who received ciprofloxacin-dexamethasone had a 90% clinical cure rate compared with the ofloxacin group at 78% ($P=.003$). The ciprofloxacin-dexamethasone group had significantly fewer treatment failures (4% vs 14%, $P=.002$), reduced median time to cessation of otorrhea (4 vs 6 days, $P=.0209$), and greater eradication of pathogens on day 18 (92% vs 82%, $P=.0061$). Each treatment was well tolerated and no serious therapy-related events were reported.

Antibiotic resistance

Bacterial resistance to antibiotics is growing and judicious use of antibiotics is advocated.[18,19] Reducing the volume of systemic antibiotics might be the most important step toward reducing resistance. Systemic antibiotics eradicate or suppress susceptible organisms from the upper respiratory tract and gut, which permits resistant strains to thrive. Topical treatment does not appear to have this effect.[20] A recent systematic review of the evidence regarding the development of antibiotic resistance with ototopical treatment indicated that antibiotic resistance is rare, although in none of the studies

was resistance the main study question.[19] Consequently, increased use of ototopical agents coupled with reduced use of systemic antibiotics might form part of the solution to the growing threat of antibacterial resistance. Topical fluoroquinolones have been suggested to be the preferable choice of treatment for tympanostomy tube otorrhea, AOM, and chronic suppurative otitis media because they have a high cure rate without systemic absorption.[20]

Ototoxicity

Topical antibiotics might cause ototoxicity because the antibiotic suspension can penetrate the middle ear through ventilation tubes or tympanic membrane perforation. *Ototoxicity* refers to injury of the cochlea or vestibular system from systemic or, more frequently, topical drugs, and can result in irreversible loss of hearing and balance. The degree of ototoxicity appears to be related to treatment duration and dose.[21-24] Some topical agents might produce middle ear damage, especially when the middle ear is free of effusion or infection.[25] Patients should discontinue using ototopical drops if they experience symptoms of cochlear or vestibular ototoxicity.[23]

Aminoglycosides. Topical aminoglycosides are potentially ototoxic, especially when the middle ear is open, as is the case with tympanostomy tubes.[6,26] With a perforated membrane, this risk is increased when aminoglycosides are administered for longer than 7 days or into a dry middle ear.[27] In 2002, an advisory was issued by Health Canada stating that gentamicin should not be used in patients with nonintact tympanic membranes.[28] The Ontario Medical Association issued an ototoxicity alert in 2004 informing physicians of cases of vestibular ototoxicity upon using aminoglycoside ear drops and reinforced a previous alert advising against the use of aminoglycosides in patients with tympanostomy tubes or perforation.[29]

Fluoroquinolones. The more recently developed fluoroquinolones are topical nonototoxic agents, which provide enhanced bacterial eradication and clinical cure; they have a very low rate of systemic absorption.[30-32] Ofloxacin and ciprofloxacin have been found to be safe and effective for the treatment of AOMT.[8,22] Antibiotic concentration of topical otic solutions is approximately 1000 times higher than systemic antibiotics, which contributes to superior eradication of the infective organism, thereby not contributing to substantial antibiotic resistance.[33,34] The 2005 *Anti-infective Guidelines for Community-acquired Infections* recommend 3 mg/mL of ciprofloxacin and 1 mg/mL of dexamethasone as first-line treatment.[27]

Ear cleaning

Topical antibiotics might not penetrate into the middle ear of patients with tube otorrhea; therefore, clearing the ear canal is imperative.[12] It is recommended that any exudate or debris be removed from the ear canal before instilling the topical agent; this should be followed by pumping of the tragus to achieve delivery to the middle ear.[6,9,22]

Limitations

We only searched major databases and limited our search to studies published in English; we did not conduct a search for unpublished literature on this topic. Few studies on the topic currently exist. With the exception of 2 studies,[12,13] all of the trials were sponsored by the pharmaceutical industry. Funding of research by pharmaceutical companies has the potential to bias research findings. For example, research that is funded by a pharmaceutical company is more likely to positively support the sponsor's product.[35] Publication bias, which is the increased probability that positive research results will be published compared with those results that are not positive, is a potential limitation whereby negative research findings on the topic might not have been published and therefore were not available for inclusion in the review.[36]

Conclusion

Tympanostomy tube insertion is a common procedure in North America, and otorrhea is a frequent sequela. Treatment options for AOMT include systemic or topical antibiotics. The reviewed studies are all methodologically strong and show that antibiotic treatment results in better outcomes than placebo. Topical treatment with fluoroquinolones, with or without the addition of corticosteroids, is better than using systemic antibiotics and results in less antibiotic resistance and fewer adverse effects, including ototoxicity, than other treatments do. Topical aminoglycoside agents should not be used to treat the draining ear because of potential, although rare, ototoxicity.

The addition of dexamethasone to a topical antibiotic might decrease the length of time necessary for middle ear drainage when compared with a topical antibiotic alone; however, the evidence for a superior cure rate when adding a steroid to an antibiotic solution is not strong, and the addition of the steroid to the solution increases the cost of treatment. Topical fluoroquinolones are the agents of choice for treatment of AOMT.

Competing interests

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EDITOR'S KEY POINTS

- Topical fluoroquinolone agents offer the most effective treatment for acute otitis media with tympanostomy tubes (AOMT) and result in less antibiotic resistance and fewer adverse effects, including ototoxicity, than do other treatments.
- Adding dexamethasone to a topical antibiotic might decrease the length of time necessary for middle ear drainage when compared with a topical antibiotic alone; however, the evidence for a superior cure rate is not strong, and adding the steroid increases the cost of treatment.
- Topical aminoglycoside agents should not be used to treat AOMT because of potential, although rare, ototoxicity.
- Few randomized controlled trials of treatments for AOMT have been done, and most have been sponsored by the pharmaceutical industry.

POINTS DE REPÈRE DU RÉDACTEUR

- Les fluoroquinolones topiques constituent le traitement le plus efficace des otites moyennes aiguës en présence de tubes tympaniques (OMAT), et entraînent moins de résistance aux antibiotiques et d'effets indésirables que les autres traitements, y compris l'ototoxicité.
- L'addition de dexaméthasone à un antibiotique topique pourrait permettre un drainage de l'oreille moyenne plus rapide que l'antibiotique topique seul; toutefois, les preuves d'un tel effet accélérateur sont minces et l'ajout du stéroïde accroît le coût du traitement.
- Les aminoglycosides topiques ne devraient pas être utilisés pour traiter l'OMAT en raison de leur potentiel d'ototoxicité, un effet toutefois rare.
- Peu d'essais randomisés sur le traitement de l'OMAT ont été effectués et la plupart étaient subventionnés par l'industrie pharmaceutique.

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