Editorial Commentary

Ototopical therapies for post tympanostomy tube otorrhoea in children

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Introduction

Tympanostomy tube (TT) insertion is one of the most commonly performed operations in children (1). TTs are most often inserted for the correction of hearing loss in persistent otitis media with effusion (OME) or for recurrent acute otitis media (rAOM). One in every two patients undergoing TT insertion will experience at least one episode of ear discharge (otorrhoea) (2), which has adverse effects on quality of life (3) and is a common indication for antimicrobial prescriptions (4,5).

Risk factors

Patient risk factors for developing TT otorrhoea (TTO) include young age, a history of recurrent upper respiratory tract infections, and having older siblings (2). Patients having TTs inserted for rAOM are also at greater risk of developing TTO than those with OME (2). The risks associated with water and tobacco exposure remain more contentious. Previous trials have shown little to no benefit from water precaution measures (6), resulting in current United States of America (USA) guidelines advising against routine prophylactic water precautions for children with TTs (4). Exposure to second hand tobacco smoke is a cause of upper respiratory tract inflammation and OME; however, two large retrospective studies have reported conflicting results regarding its association with TTO (2,7).

In addition to patient-specific factors, TTs themselves determine the risk of TTO. A 2018 randomised controlled trial of 378 children comparing four types of TT found that silicone tubes had a significantly longer otorrhoea-free interval after insertion than fluoroplastic tubes, although there was no difference in overall infection rate (8). In this trial, tube shape (short versus long) did not affect number or timing of infections. *Ex vivo* studies of TTs have shown biofilms—adherent bacterial communities encapsulated in an extracellular polymer matrix—favour particular sites in several common TT designs (9). In particular, perpendicular junctions of tubes seem particularly vulnerable to biofilm formation, suggesting that geometric modifications to TT designs could be beneficial. Other avenues of active research include TT material modifications and antimicrobial coverings to inhibit biofilm formation (9).

Microbiology of TTO

The microbiology of TTO tends to reflect the organisms found in middle ear infections, which are predominantly bacterial in nature. Common bacteria can be thought of as either typically nasopharyngeal (for example *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*) or external ear canal in origin (for example *Pseudomonas aeruginosa* and *Staphylococcus aureus*). The

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former is typically associated with younger children and the latter with older children (10,11).

Viral co-infection is also common. In one small study viral co-infection was present in two thirds of children with TTO; picornavirus was the most prevalent (41%), followed by rhinovirus (20%) and enterovirus (10%) (12). Fungal causes of TTO are typically preceded by antibiotic therapy; common organisms include candida albicans, candida parapsilosis, and aspergillus fumigatus (13).

Prophylactic antimicrobials

In order to reduce TTO some clinicians historically advocated the routine prescription of a course of topical antimicrobial therapy following TT insertion. A cochrane review of 15 randomised studies identified that whilst a post operative course of topical antimicrobial therapy does reduce the incidence of otorrhoea, the effect is not greater than saline rinses combined with a single intra-operative dose of a topical antimicrobial agent, and the former involves greater financial cost and confers an increased risk of antimicrobial resistance (14). Therefore, current USA guidance advises against the routine prescribing of a course of topical antimicrobial therapy following TT insertion. However, a single intra-operative dose immediately following TT placement may be used at the surgeon's discretion (4).

Treatment of TTO

Whilst prolonged courses of topical antimicrobial therapies are of limited value for the prophylaxis of TTO, they have a key role in treating episodes of TTO when it occurs. A large trial of children with TTO published in 2014 found evidence strongly in support of topical antimicrobial treatment over other approaches to treatment: only 5% of patients had persistent otorrhoea after topical therapy versus 44% with oral antimicrobials and 55% with active observation alone (15). This study and others were included in a large network meta-analysis in 2017 by Steele *et al.*, which further confirmed the greater efficacy of topical over oral antimicrobial therapy (odds ratio of 5.3; 95% confidence interval: 1.2–27) (16). This is reflected in the recently updated 2022 American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) guidelines, which recommend the use of topical rather than oral antimicrobial therapy for episodes of TTO (4). The Steele *et al.* meta-analysis also demonstrated that topical antimicrobial-glucocorticoid combinations are more effective than topical antimicrobial monotherapy alone.

Although topical delivery is the favoured route of treatment for TTO, ear drops typically require several applications per day, which many individuals find difficult, leading to poor compliance. One study based on topical treatments for otitis externa in adults found that alarmingly only 40% of patients successfully applied ear drops with an error rate of less than 25% after 3 days, and this dropped to only 32% at 11 days (17). Similar studies of the adherence to topical ear drops amongst children do not exist, but factors such as potentially poor understanding of reasons for treatment and dependence on caregivers to administer the medication would suggest that compliance is possibly lower in this group (18).

Novel agents for TTO

Otic gels

One method to overcome the challenge of poor compliance is to reduce the frequency required for topical therapy application, but without compromising efficacy. Ciprofloxacin otic gel (COG) is a single-application agent, which slowly releases ciprofloxacin over time. COG has been trialed as a prophylactic agent against TTO in a study that directly compared COG to TT insertion alone (without any topical antimicrobial agent) and demonstrated a lower rate of otorrhoea in the COG group (19). This study did not look at the use of COG in treating TTO, which would be a valuable area for further research. It is noteworthy that the COG formulation presented above is solely an antimicrobial agent without glucocorticoid. However, it is understood from the Steele *et al.* meta-analysis that the addition of glucocorticoid to antimicrobial agents might result in greater efficacy for the treatment of TTO (16). Ku *et al.* recently published a pre-clinical study of a ciprofloxacin-dexamethasone combination hydrogel, which has demonstrated safety *in vivo* in an animal model, but confirmation of efficacy in human clinical trials is awaited (20).

Targeted biofilm disruption

Biofilms are known to form on TTs, helping protect bacteria from both antimicrobial treatments and the host immune system, in turn contributing to TTO (21). In addition to TT design modifications to prevent biofilm formation,

targeted treatments to degrade biofilms are under development. One example is the use of modified release antimicrobial pellets, which have shown promise in biofilm eradication i*n vitro* (22). More recent efforts have used monoclonal antibodies against DNABII proteins, which are integral to the structure of the extracellular matrix, and this strategy has been shown to be effective in a chinchilla model (23). Other approaches include using photo-dynamic therapy (PDT), in which excitation of a light sensitive drug releases cyotoxic singlet oxygen molecules (24). This has shown efficacy in otopathogen-specific biofilms, but as with the other anti-biofilm treatment approaches described, is yet to enter routine clinical practice.

Future research into treatment options for TTO

Future research must continue to examine the dynamically changing microbiology of TTO as this can be changed by the introduction or modification of national vaccination programmes, amongst other factors, and will likely lead to changes in disease aetiology and optimal treatment strategies (25).

It is also important to remain cognisant that certain patient groups are at higher risk of TTO. Many trials to date consider TTO as a discrete entity, but it is important that future research on the role of ototopical therapies, including otic gels and agents for the disruption of biofilms, specifically consider efficacy in these at-risk patient groups; in order to evaluate whether particular agents are more or less effective in these selected circumstances, such as stratifying by patient age or operative indication. Such differences could enable a personalised approach to treatment for the most at-risk patients of TTO and offer a welcome addition to the presently constrained range of treatment options.

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