Microbial otitis media: recent advancements in treatment, current challenges and opportunities

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Abstract

Otitis media (OM) is a common disease affecting humans, especially paediatric populations. OM refers to inflammation of the middle ear and can be broadly classified into two types, acute and chronic. Bacterial infection is one of the most common causes of OM. Despite the introduction of vaccines, the incidence of OM remains significantly high worldwide. In this mini-review article, we discuss the recent treatment modalities for OM, such as suspension gel, transcutaneous immunization, and intranasal and transtympanic drug delivery, including therapies that are currently undergoing clinical trials. We provide an overview of how these recent advancements in therapeutic strategies can facilitate the circumvention of current treatment challenges involving preadolescence soft palate dysfunction, biofilm formation, tympanic membrane (ear drum) barrier and the attainment of efficacious drug concentrations in the middle ear. While traditional first-line immunization strategies are generally not very efficacious against biofilms, new technologies that use transdermal or intranasal drug delivery via chitosan–PsaA nanoparticles have shown promising results in experimental animal models of OM. Sustained drug delivery systems such as penta-block copolymer poloxamer 407–polybutylphosphoester (P407-PBP) or poloxamer 407 (e.g. OTO-201, with the brand name ‘OTIPRIO’) have demonstrated that treatments can be reduced to a single topical application. The emergence of effective new treatment modalities opens up promising new avenues for the treatment of OM that could lead to improved quality of life for many children and their families.

INTRODUCTION

Otitis media (OM) is the acute presentation of otorrhea or the protrusion of the tympanic membrane in conjunction with signs of systemic illness and inflammation of the middle ear. It can be classified as acute OM (AOM) or chronic OM (COM) [1]. OM is the most common reason for antibiotic prescriptions and the most common reason for children to visit a physician [2, 3]. OM with effusion (OME) can occur post-OM or post-upper respiratory tract infection. The characteristic that distinguishes OM from OME is fluid accumulation in the middle ear cavity without systemic signs of infection [4]. Children who experience OME have a higher likelihood of infection due to pathogens such as Streptococcus pneumoniae, Moraxella catarrhalis and adenovirus [5]. If such infections are not adequately treated, OM may progress to chronic suppurative OM (CSOM), which characteristically includes chronic otorrhea (more than 2 weeks) and perforation of the tympanic membrane, and can ultimately result in permanent hearing loss [6, 7].

S. pneumoniae, nontypeable Haemophilus influenzae (NTHi) and M. catarrhalis continue to be the bacterial pathogens that are most frequently isolated from AOM [8, 9]. On the other hand, Staphylococcus aureus and Pseudomonas aeruginosa are the pathogens that are most commonly associated with CSOM [10–15]. Besides these aerobic microbes, fungi and anaerobic bacteria have been correlated with OM/CSOM [16]. The anaerobic bacteria isolated from OM/CSOM patients include Clostridium spp., Peptococcus spp., Prevotella melaninogenica and Fusobacterium spp. Anaerobic bacteria may play a more meaningful role in patients with COM. Specifically, anaerobic Gram-positive cocci and Bacteroides spp. are the most frequently
cumulative incidence of AOM in the post-PCV era (2006–2016) is as follows. One or more episode of AOM: 23% at ≤1 year, 42% at ≤2 years and 60% at ≤4 years [22]. This can be compared with data from the pre-PCV era (1989), which indicate that the cumulative incidence of AOM was as follows. One or more episode of AOM: 62% at ≤1 year and 83% at ≤3 years [23]. Despite the apparent decline in the cumulative incidence of AOM in the post-PCV era, there has been a marked increase in β-lactamase-producing H. influenzae since 2012 (discussed below). Further, a potentially confounding variable was introduced between the pre- and post-PCV eras, in that more stringent criteria were introduced for AOM diagnosis. These new criteria might have led to overestimation of the preventive impact of PCV.

The continual change in relevant bacterial pathogens will likely demand protection from antigens such as pneumococcal surface protein A (PspA), pneumococcal surface protein C (PspC), pneumolysin, pneumococcal pilus proteins and trivalent protein antigen [21]. Furthermore, in the 1990s OM cases were more often due to S. pneumoniae (48% of cases), but the paradigm shifted in the early 2000s to feature H. influenzae more often (57% of cases). Further, the strains of H. influenzae that are most attributable to OM are more likely to be β-lactamase producing, making them less susceptible to killing by penicillin [24].

CURRENT TREATMENT MODALITIES

After vaccination, antibiotics are most commonly used for the treatment of OM. The first-line therapy for patients without a history of OM is oral amoxicillin (Table 1). For children with a history of OM, those with concurrent purulent discharge, or those who have been treated with β-lactam antibiotics in the past 30 days, it is recommended to include a beta lactamase inhibitor, such as clavulanate, in the amoxicillin regimen [25]. Mild delayed hypersensitivity to penicillin is not uncommon. For children who experience non-IgE-mediated side-effects (such as anaphylaxis and Stevens–Johnson syndrome, amongst others), alternative medications include cefdinir, cefpodoxime, cefuroxime and ceftriaxone [25, 26]. Alternatively, patients with a serious IgE-mediated, delayed hypersensitivity to penicillin may take azithromycin, clarithromycin, erythromycin/sulfisoxazole, or clindamycin [25]. If the tympanic membrane has also been ruptured, topical antibiotics are the preferred modality of treatment [25].

Amoxicillin is considered to be the most cost-effective therapeutic modality for AOM [27]. For symptomatic pain relief, ibuprofen, acetaminophen, or topical lidocaine may be used [25]. Despite its widespread availability, convenience and affordability, numerous barriers can prevent effective treatment. Generally, oral antibiotics have poor diffusion into the middle ear and the pathogens often form biofilms, which further reduces the efficacy of antibiotic therapy [28, 29]. While the data suggest that 95% of physicians use antibiotics to treat AOM, the American Academy of Pediatrics (AAP) standards allow...
Table 1. A summary of otitis media treatment modalities

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
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<tbody>
<tr>
<td>Standard of care</td>
<td>Cost-effective</td>
<td>Poor diffusion to middle ear</td>
<td>[25]</td>
</tr>
<tr>
<td>Drug: amoxicillin or amoxicillin/clavulanate</td>
<td>Availability</td>
<td>Hypersensitivity</td>
<td></td>
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<tr>
<td>Transcutaneous immunization (TCI)</td>
<td>Mucosal and systemic immunity</td>
<td>Discomfort to the child</td>
<td>[70], [63]</td>
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<tr>
<td>Intranasal vaccination using ionotropic gelation with chitosan–PsA nanoparticles</td>
<td>Mucosal delivery</td>
<td>Immunization strategy only</td>
<td>[72, 74]</td>
</tr>
<tr>
<td>Post-tympanostomy tube treatment topical therapy utilizing thermostensitive suspension gel with ciprofloxacin</td>
<td>Avoidance of elimination by hepatic or gastrointestinal metabolism</td>
<td>Difficult to place outside of operating room</td>
<td>[62, 76, 77]</td>
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<tr>
<td>Transtympanic antibiotic delivery using a penta-block copolymer of P407-PBP</td>
<td>Readily deliverable and efficacious</td>
<td>Potential for tissue damage</td>
<td>[83]</td>
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for an observation period of 48 to 72 h to permit a spontaneous clearing of the otitis media infection. This strategy has been termed ‘watchful waiting’ [30–32]. More recently, it has been demonstrated that watchful waiting, which is defined as no antibiotics and symptomatic treatment only, is superior in terms of both cost savings and patient outcomes, in addition to preventing the emergence of antibiotic resistance [4, 33–35].

CHALLENGES AND BARRIERS TO ANTIBIOTIC DELIVERY

The aforementioned challenges that stem from current immunization schedules, changes in microbial prevalence and patient adherence all emphasize the need for a single-dose, non-invasive preventative therapy. In this section, we briefly summarize the difficulties encountered in drug delivery for OM.

Identification of pathogens

The ability to identify organisms and monitor their frequency is an inherent challenge that is perhaps most central when targeting the pathogens associated with OM and developing antibiotic delivery mechanisms. Diagnosing AOM is further complicated because the disease does not have a gold standard diagnostic test [36]. Hence, clinicians are encouraged to acquire a culture through the use of tympanocentesis [36].

A primary difficulty in the accurate identification of OM-associated bacteria can stem from the underlying requirement for rigid and consistent laboratory procedures [37]. Even when using laboratory methods such as tympanocentesis to identify either anaerobic or aerobic bacteria, other bacteria that reside in the ear canal can potentially contaminate specimens [38]. A study attempted to maximize culture accuracy by removing exudate from the external ear canal prior to needle aspiration [39]. Even when proper procedures for culturing aerobic and anaerobic bacteria are followed, it can be difficult to eliminate the possibility of a culture becoming contaminated with a host’s natural flora [5]. When clinicians are unable to eliminate pathogens from the external ear prior to attaining a sample, they are often limited to a criterion for positive test results that only includes already-known pathogens [38]. With narrowed criteria, sensitivity can suffer, as such methods exclude commonly found skin flora at the potential cost of excluding other potentially causative pathogens. At the other end of the spectrum, technologies such as polymerase chain reaction (PCR) offer superior sensitivity to observe the association of various immunization regimes with predominant bacterial and viral pathogens. Even when cultures are negative, PCR allows for the observation of pathogens such as *M. catarrhalis* and *S. pneumoniae* [37]. While PCR can increase both sensitivity and specificity [40], there is a need to develop a common consensus among researchers concerning the analysis of PCR results [41].

Antibiotic resistance

One of the primary forms of bacterial resistance associated with OM is β-lactamase-producing bacteria. In a cross-sectional study of nearly 13 000 children with AOM, nasopharyngeal carriage was analysed from 2001 to 2016 in an effort to associate trends with the introduction of the PCV13 vaccine. During this period, the overall presence of *S. pneumoniae* was found to have decreased by 18.2 %. Among all children found to be *S. pneumoniae* carriers, β-lactamase-producing *S. pneumoniae* strains accounted for only 0.8 % of cases, and only 0.4 % of cases among all children. Analysis of *H. influenzae* strains demonstrated that beginning in 2012, β-lactamase-producing *H. influenzae* began increasing and now comprise about 23.6 % of the *H. influenzae* strains isolated from OM cases [42]. Due to the emergence of antibiotic resistance, there is a need to develop novel treatment modalities beyond antibiotic therapy.

Inability of vaccines to effectively control OM

While the administration of vaccines during infancy has been demonstrated to result in a small reduction in AOM...
frequency, such vaccines are more beneficial in reducing OM recurrence or reducing the requirement for tympanostomy tube placement [43]. For example, the heptavalent pneumococcal conjugate vaccine (PCV7) has been associated with a reduction in pneumococcal carriage and increased AOM infections [44]. Despite such therapeutic strategies, OM infections are still commonly associated with bacteria such as S. pneumoniae, NTHi and M. catarrhalis [45]. In countries such as France [46], Spain [47] and the United States [48], the PCV7 immunization schedule has been associated with a shift from S. pneumoniae to non-vaccine pneumococcal serotypes, such as NTHi. Proper detection and monitoring of OM pathogens will facilitate the implementation of new vaccines that deliver resistance against the complex otopathogens of the middle ear [49].

**Eustachian tube dysfunction**

Dysfunction of the Eustachian tube is perhaps the important factor in the pathogenesis of AOM [50]. In childhood, before the soft palate muscle sling descends relative to the Eustachian tube orifice, the patency of the Eustachian tube can be hindered [50]. Such anatomic tubal dysfunction is not only thought to be the primary factor responsible for a higher incidence of AOM among children, but it also highlights the necessity of designing immunization strategies that are suitable for children.

**Microbial biofilm formation**

Another challenge that prevents efficient drug delivery for the treatment of OM is biofilm formation [51–53]. Biofilms can be detected by middle ear mucosal biopsy. After effusion from the middle ear has been obtained, PCR, microscopy and immunostaining can detect biofilm formation. Specifically, BacLight, fluorescence in situ hybridization (FISH) and immunostaining are useful for the identification of biofilms in bacteria such as S. pneumoniae and H. influenzae [29]. The formation of biofilms by otopathogens leads to the evasion of the host immune system as well as antibiotic resistance [54]. The pathophysiology of upper aerodigestive infections is increasingly in association with antibiotic resistance [55–58]. As the biofilm aggregates, bacteria attach to a surface and can survive with decreased metabolic and reproductive rates. The barrier that biofilms produce is difficult to penetrate with antibiotics and identification is often hindered due to the challenge of culturing biofilms. Evidence supporting the pathogenic effect of biofilms is primarily derived from studies that have observed their presence in typanostomy tubes [59] and cholesteatomas [60].

**Inability of drugs to reach the site of OM in the ear effectively**

The inherent characteristics of intestinal absorption and the first-pass effects from the liver dramatically reduce the effective drug concentrations found in the desired pharmaceutical effect site [61, 62]. The reduction in tissue drug concentration, along with the potential for adverse side-effects from the systemic distribution of oral medications, can make oral therapies less than desirable [61].

**Patient adherence**

Finally, whether oral, topical, or vaccination therapies are being used, patient adherence can be a potential barrier to nearly all pharmaceutical treatment regimens [63]. If ear-drops are being utilized, particularly in the case of post-typanostomy tube surgery, a caregiver may have no way of identifying whether topical ear drops have been delivered to the intended therapeutic target [64]. Likewise, a child may complain of ear pain, which precludes topical application [61]. Alternatively, patients may discontinue antibiotics prematurely at the onset of symptom resolution. Even routinely administered vaccinations can be inadvertently overlooked.

Although substantial data have been gathered on the role of respiratory virus–bacterial co-infections and their association with the pathogenesis of AOM, the influenza vaccines are the only currently effective measures against respiratory infections [65–67]. Vaccinations such as trivalent inactivated influenza vaccine (TIV) and live-attenuated influenza vaccine (LAIV) have been demonstrated to be effective preventative measures against both influenza and AOM/influenza morbidity [19].

Despite the difficulty of maintaining yearly influenza vaccinations among certain patient populations, recent advances in single-dose, non-invasive treatments and preventative measures appear to be more promising than previously thought. In the next section, we will discuss the recent advancements regarding drug delivery for the treatment of OM, as summarized in Table 1.

### OPPORTUNITIES: TREATMENT MODALITIES OF PROMISE

**Transcutaneous immunization**

A natural first step in combating pathogens is to halt growth before it begins. Vaccination strategies that involve transcutaneous immunization (TCI) offer a noninvasive paradigm to elicit an immune response within the skin’s epidermis and dermis (Fig. 1) [68, 69]. This is relevant pathologically because TCI induces both mucosal and systemic immunological responses. TCI is desirable to clinicians because it can be delivered without needles. Needleless delivery reduces the risks associated with vaccine delivery and hazardous waste, is favourable for patient adherence and is likely to reduce expenditure on delivery modes and standard formulations [70].

A recent study demonstrated the effectiveness of TCI in providing protection against OM. Underscoring the impact of their work, a viral–bacterial confection model was used, along with OM induced by NTHi [63]. The vaccine was constructed from adhesive proteins and mediators of biofilm, including chimV4, integration host factor and recombination soluble PilA (rsPilA). The latter is derived from PilA, the majority subunit of NTHi’s type IV pilus [71].
The prospective immunogens were then admixed with an adjuvant, LT(R192G/L211A), a heat-labile enterotoxin double mutant derivative from *Escherichia coli*. When the outcomes were measured via otoscopy and typanometry, the OM signs were significantly reduced among animals that received the vaccine when compared to animals that received adjuvant-only treatment. The vaccine efficacy was determined to be between 64 and 77%. While perhaps the most non-invasive option available, TCIs are typically placed for 1 day, a time period that might be difficult, depending on the restlessness of the child.

**Intranasal vaccination**

Intranasal vaccination has the potential to circumvent the requirement for at-home patient adherence, while offering immunological advantages. Strains such as pneumococcus enter the nasopharynx and induce AOM after entering the Eustachian tube [72]. If pneumococcal colonization leads to entry into the bloodstream, bacteraemia and sepsis can result. For this reason, it is imperative for vaccination strategies to address immune responses, both systemically and at the level of the mucosa [72]. Intranasal vaccination offers a promising modality to induce both mucosal and systemic immunity, although the permeability of the epithelial membranes that line the mucosa is low [73].

Therefore, the ability of a vaccine to be appropriately delivered to the mucosa is implicit in intranasal delivery. One promising intranasal vaccine delivery system has utilized ionotropic gelation [74] with tripolyphosphatatechitosan–PsA to prepare chitosan–PsA nanoparticles [72]. Such a preparation is advantageous because of its ability to harness the host’s mucosal and systemic immune system, resulting in heightened protection from pneumococcal strains of AOM [72]. Compared to control mice that were immunized with naked PsA, mice that received the chitosan–PsA vaccine demonstrated reduced levels of IFN-γ, IL-17A and IL-4 in their spleen lymphocyte cells, and they were found to have significantly enhanced levels of specific systemic IgG and mucosal IgA antibodies [72]. Even more clinically relevant, the chitosan–PsA vaccine recipients were found to have improved OM responses to pneumococcus serotype 14 [72]. In murine models, intranasal vaccinations have been expanded to demonstrate the prevention of bacterial and viral agents that result in OM [75]. While intranasal vaccination strategies appear to be promising when considering the pathogens responsible for AOM, further clinical trials are needed in order to decipher the role of intranasal vaccination in preventing the occurrence of OM.

**Topical therapies**

While transdermal or intranasal therapies may be helpful as an immunization strategy, topical therapies offer a practical mechanism for OM prophylaxis in the post-surgical environment. The current clinical practice guidelines recommend the topical application of antibiotics in place of oral therapies after tympanostomy tube placement [76]. Clinical trials have examined the post-tympanostomy tube treatment options, comparing, for example, oral antibiotics, such as amoxicillin or amoxicillin clavulanate, and eardrop mixtures of ofloxacin, ciprofloxacin or ciprofloxacin/dexamethasone [77]. As topical therapies can be delivered at the site of inflammation, they avoid elimination by the hepatic and gastrointestinal metabolism and they have been demonstrated to attain tissue concentrations that are over 1000 times higher than those for the oral alternatives [78]. OTIPRIO is the branded version of OTO-201, which is a suspension of ciprofloxacin in poloxamer 407 that utilizes thermosensitive suspension gel with ciprofloxacin [61]. OTIPRIO is the first FDA-approved, physician-
administered, single-dose treatment for post-tympanostomy tube otorrhea. This single-treatment therapy is ideal if a tympanostomy tube has been placed, although it is potentially difficult to deliver outside the operating room.

**Delivery of drugs through transtympanic route**

Trans-tympanic delivery offers a potentially more viable option for local drug delivery for the treatment of OM in the outpatient setting (Fig. 2). Since 2006 the FDA has approved numerous bacteriophage-based products, although none have been approved for OM. The Wright group performed the first clinical trial to demonstrate safe and efficacious treatment with a therapeutic bacteriophage preparation (Biophage-PA) against *P. aeruginosa* [79]. The ability of a phage to pass through the tympanic membrane appears to be determined by the amino acid sequences that are displayed on the surface of the phages [79]. A study investigated the ability of 22 unique phage clones to pass through the tympanic membrane [58]. Central residue positivity and polarity can demonstrate phage preference for penetrating the trans-tympanic membrane [80]. Perhaps equally important is the fact that the peptides that show enhanced trans-tympanic transport demonstrate this potential independently of phage attachment and molecular size [81].

In experimental animal models, phages have been demonstrated to deliver a payload to the middle ear cavity with minimal or no delivery into the inner ear when armed with specific peptide sequences [82]. Such precise delivery mechanisms are not only useful in maximizing the drug effect on the target organ, but they also mitigate toxicity to hearing-related structures [82]. The most recent efforts to improve middle ear drug delivery have focused on optimizing...
peptide sequences that are actively transported across the tympanic membrane [82]. Out of a randomly selected set of 12-mer and 18-mer peptides, those that displayed the highest rates of trans-tympanic membrane transport appeared to have characteristic placement of aliphatic and aromatic residues. Despite these trends, no other amino acid-specific characteristics have been identified.

Other forms of trans-tympanic antibiotic delivery against OM that do not use phage therapy have also been investigated using a penta-block copolymer of poloxamer 407-polylbutylphosphoester (P407-PBP) [83]. This therapy demonstrated the ability to flow readily during application and also formed a hydrogel on the tympanic membrane readily. When tested against an NTHI challenge, the delivery system was found to completely eradicate AOM in 10 out of 10 mice (100%). This result was compared with the result for a control group that received 1% ciprofloxacin, in which only 63% of mice cleared the infection. Further studies employing sustained drug delivery systems will help in developing novel treatment modalities for OM.

**Biofilms: unique therapeutic opportunities**

Due to a number of the aforementioned properties of biofilms, traditional topical antibiotics are ineffective [54, 84]. Treatments such as gentian violet and mupirocin are difficult to deliver and ototoxic [85]. Therapies that target biofilms have typically focused on disrupting their adherence and proliferation via biochemical or electromechanical mechanisms [86]. Biochemical mechanisms target specific molecular properties [87], enhance delivery, [88] and improve quorum sensing [58]. Treatments such as pulsed laser therapy have been demonstrated to dislodge biofilm adhesiveness. Drug delivery mechanisms against biofilms that appear to hold potential include the electromagnetic, the ultrasonic and phototherapy [88], and these need to be explored in future studies.

**CONCLUSION AND FUTURE DIRECTIONS**

This paper reviewed novel immunization and treatment modalities targeting OM. Despite widespread availability, standard oral antibiotic therapies are often ineffective due to numerous shortcomings and obstacles, such as the inability to reach the site of OM in the ear at optimal concentrations and biofilm formation. With the recent demonstration of the in vivo effectiveness of TCI immunization, a small circular band-aid can be used to deliver vaccines [63]. This would be a clinical paradigm shift for the effective treatment of OM. This noninvasive and therapeutically simple treatment has the potential to achieve higher drug concentrations through localized administration, avoiding the requirement for systemic drug saturation and potentially delivering a single administered treatment, while it would certainly be preferable for clinicians and patients. While the current success of trans-tympanic membrane delivery is promising, further research is necessary to elaborate the mechanisms that mediate trans-tympanic membrane transport. In addition, there is a need to understand the pathogenesis of OM, especially CSOM, which will provide novel clues to develop effective preventive and therapeutic strategies. There is still an unmet medical need for the nonsurgical delivery of drugs into the middle ear for the effective treatment of OM. The emerging fields of nanomedicine and phage therapy will help in the development of novel and effective treatments for OM. Whether targeting acute illness or immunization – on either individual or population scales – it is likely that a combination of traditional and recent treatment modalities will be pivotal in the next generation of OM therapeutics.

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