International Journal of Pediatric Otorhinolaryngology 78 (2014) 1433–1438

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Strategies to prevent biofilm-based tympanostomy tube infections

James C. Wang [a,*], Abdul N. Hamood [b], Charles Saadeh [a], Michael J. Cunningham [c], Michael T. Yim [d], Joehassin Cordero [e]

[a] School of Medicine, Texas Tech University Health Sciences Center, 3601 4th Street STOP 8312, Lubbock, TX 79430, USA
[b] Department of Microbiology & Infectious Diseases, Texas Tech University Health Sciences Center, Lubbock, TX, USA
[c] Department of Otolaryngology and Communication Enhancement, Children's Hospital Boston, Boston, MA, USA
[d] Department of Otolaryngology – Head and Neck Surgery, Baylor College of Medicine, Houston, TX, USA
[e] Division of Otolaryngology, Department of Surgery, Texas Tech University Health Sciences Center, Lubbock, TX, USA

ARTICLE INFO

Article history:
Received 20 March 2014
Received in revised form 9 May 2014
Accepted 20 May 2014
Available online 30 June 2014

Keywords:
Otitis media
Tympanostomy tubes
Bacterial biofilms
Medical device coatings
Antimicrobial agents

ABSTRACT

Objective: To review the potential contributory role of biofilms to post-tympanstomy tube otorrhea and plugging as well as the available interventions currently utilized to prevent biofilm formation on tympanostomy tubes.
Data sources: A literature review was performed utilizing the MEDLINE/Pubmed database from 1980 to 2013.
Review methods: Electronic database was searched with combinations of keywords "biofilm", "tympanostomy tube", "ventilation tube", and "post-tympanostomy tube otorrhea".
Results: Two of the most common sequelae that occur after tympanostomy tube insertion are otorrhea and tube occlusion. There is an increased evidence supporting a role for biofilms in the pathogenesis of otitis media. In this review, we have shown a multitude of novel approaches for prevention of biofilm associated sequelae of otitis media with effusion. These interventions include (i) changing the inherent composition of the tube itself, (ii) coating the tubes with antibiotics, polymers, plant extracts, or other biofilm-resistant materials, (iii) tubal impregnation with antimicrobial compounds, and (iv) surface alterations of the tube by ion-bombardment or surface ionization.
Conclusion: Currently, there is not one type of tympanostomy tube in which bacteria will not adhere. The challenges of treating chronic post-tympanostomy tube otorrhea and tube occlusion indicate the need for further research in optimization of tympanostomy tube design in addition to development of novel therapies.

1. Tympanostomy tube related complications

1.1. Post-tympanostomy tube otorrhea (PTTO)

PTTO is active drainage through an existing tympanostomy tube (TT) which can lead to tube occlusion and discomfort [1]. Pathogenic bacteria may attach onto the abiotic surface of tympanostomy tubes and continue to develop to a critical mass where they may detach and contribute to PTTO. PTTO is associated with several factors including the (i) onset of drainage, (ii) patient's age, and (iii) previous exposure to antibiotics [2].

PTTO may be early or late in onset. Early-onset PTTO occurs within two weeks of tube placement in approximately 10–20% of children who undergo insertion of tympanostomy tubes [2]. Such drainage is attributed either to preexisting middle ear infection or contamination of the external auditory canal during surgery [2]. Late-onset PTTO (>2 weeks after placement) occurs at least once in approximately 30% of children with tympanostomy tube placement, with about 7% developing recurrent PTTO. This is most likely due to upper respiratory tract infection and less frequently due to middle ear contamination secondary to water exposure. Recurrent tympanostomy tube otorrhea is defined as distinct episodes of PTTO followed by periods without otorrhea [2].

In addition, PTTO can be described as acute (lasting <6–8 weeks) or chronic (lasting >6–8 weeks). In children younger than two years of age, acute PTTO is usually caused by the same otopathogens as acute otitis media (AOM) including *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* [3–6]. In older children, acute PTTO is more likely caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa* [3,4,7]. In chronic PTTO, community acquired methicillin-resistant *S. aureus* (MRSA) and multidrug resistant *S. pneumoniae* are potential causes

* Corresponding author. Tel.: +1 806 743 2370; fax: +1 806 743 2374.
E-mail address: J.Wang@ttuhsc.edu (J.C. Wang).

http://dx.doi.org/10.1016/j.ijporl.2014.05.025
0165-5876/

of PTTO refractory to antibiotic therapies [8,9]. As expected, children who have received multiple courses of antibiotics to treat PTTO will have an increase in drug-resistant organisms [10].

If tympanostomy tube occlusion occurs due to PTTO, the effect of topical antibiotics may be compromised [11]. Occasionally it is necessary to remove the tympanostomy tube, resulting in additional exposure to general anesthesia and increased costs incurred to the patient and patient's family. The challenges of recalcitrant otorrhea due to chronic PTTO suggest that new developments in therapies are necessary, as preventing PTTO is highly desirable.

1.2. Tube occlusion

The rate of occlusion or plugging of tympanostomy tubes is reported to range from 6.9 to 36% [2,4,12]. This occlusion can be due to otorrhea, cerumen, mucus, dried blood or granulation tissue. Cerumen is suggested to be the least likely cause of TT plugging because it is produced in the cartilaginous part of the external auditory canal and thus unlikely to move retrograde against the natural movement of the canal epithelium [5]. Aural polyp formation secondary to chronic infection can likewise occlude TT lumen and necessitate tube removal [13]. Since TTs are inserted for a finite period of time, increasing time to occlusion has been an area of recent interest. TT lumen inner diameter (ID) may play a role in the time to occlusion. It has previously been shown *in vitro* that smaller ID tubes result in faster occlusion. When circumvention of TT occlusion is critical, larger ID tubes may be warranted [14]. *In vitro* studies have shown that there is increased time to occlusion with coated TTs versus uncoated [12]. However, differences between various coatings, such as human serum albumin, polyvinylpyrrodilone, and phosphorylcholine were not significant. *In vivo* studies are needed to assess differences with time to occlusion.

Mucoid effusion may result in increased occlusion because of incomplete evacuation of fluid. In addition, it has been postulated that the incidence of mucoid PTTO is common and likely the reason for tympanostomy tube occlusion [5]. Although blood may be mixed with mucoid effusion, it has been suggested that it is not the main basis of TT occlusion [5]. Recently, bacterial infections and biofilm formation on tympanostomy tubes have been proposed to contribute to TT plug formation [6].

Once plugged, the functionality of the TT to ventilate the middle ear cavity is lost. Current options for treatment include the use of ototopical drops to clear the obstruction. However, if plugging persists, the patient may need to be brought to the operating room to unblock the occlusion using a small metal suction catheter or to remove the tube [15]. This complication can cause considerable morbidity, requiring aggressive medical therapy, which if unsuccessful, culminates in additional surgery to remove the non-functional tube.

2. Biofilm development on tympanostomy tubes

Biofilms are a complex microbial community in which multiple species of bacteria co-exist in a matrix of extracellular polysaccharide substance. Recent research implicates biofilms to play a significant role in the pathophysiology of recurrent AOM and chronic otitis media with effusion (OME) [16]. The common AOM pathogens *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae* all have been implicated in biofilm development and formation [7,9,17]. Co-infection with *H. influenzae* and *S. pneumoniae* has been demonstrated through fluorescent in situ hybridization (FISH) of bacterial biofilms of middle ear mucosa biopsy specimens [9]. The more chronic otitis media (OM) pathogenic organisms *S. aureus* and *P. aeruginosa* have also been associated with OM biofilms [18]. Traditional antibiotics are capable of killing planktonic free-floating cells, but the microstructure of biofilms contributes to the inability of these drugs to work effectively. The heterogeneity of the microenvironment may also affect the efficacy of various antibiotics [16]. Aerobic, facultative anaerobic, and obligate anaerobic bacteria may occupy different regions of the biofilm due to these physiological differences in biofilm composition.

2.1. Analysis of biofilms on tympanostomy tubes

To date, the majority of studies investigating biofilm characteristics and formation have utilized *in vitro* methods. The two main *in vitro* models for studying biofilm formation on tympanostomy tubes include (i) a static model where tubes are suspended on a steel hook or submerged in microtiter plates with media [19] and (ii) a dynamic model in a flow-cell or drip-flow chamber [20]. In the static model, ventilation tubes are submerged in media loaded into each well of the plate. In the dynamic flow-cell and drip-flow models, the tubes are submerged in a chamber in which fluid flows from a nutrient media source into a waste container.

Direct observation by scanning electron microscopy (SEM) or FISH in combination with confocal laser scanning microscopy (CLSM) has traditionally been used when assessing biofilm formation [21–23]. However, both of these imaging techniques have limitations such as having to fix the bacteria on the substrate or poor depth of penetration of the laser. Efforts have been made in combining various imaging techniques to generate a more complete understanding of biofilm structure [24,25]. Only a few studies have been published to date specifically regarding the imaging of biofilms related to otitis media and tympanostomy tubes. All studies used SEM, CLSM, or a combination of both [8,18,26–29].

3. Strategies to inhibit biofilm development on tympanostomy tubes

Thus far, research has focused on modulating two major variables: (i) changing the inherent composition of the tube itself or (ii) coating the tubes with antibiotics, plant extracts or other biofilm-resistant materials. Table 1 provides a summary of these interventions.

3.1. Tympanostomy tube coatings

3.1.1. Antibiotic

To prevent bacterial colonization, many researchers have attempted to coat tympanostomy tubes with antibiotics. An *in vitro* study has demonstrated tubes coated with piperacillin-tazobactam to be resistant to biofilm development by ciprofloxacin-resistant *P. aeruginosa* (CRPA) after a six day incubation [19]. Using similar methodology, vancomycin coated tubes have been made resistant to MRSA biofilm formation [30]. Such studies utilizing antibiotic coated tympanostomy tubes have been limited in scope and warrant further research including *in vivo* models. The possibility that antibiotic coated tubes may induce the emergence of antibiotic resistant bacterial strains requires further investigation.

There has also been an interest in modifying tympanostomy tubes in order to allow for long-term release of antimicrobials. A monolithic nonporous polymer tube consisting of solidified polymer melts (Elvax and Polyurethane) and antibiotics (Ciprofloxacin, Usnic acid, polyhexylmethylbiguanide), which allows for two stages of antibiotic release, has been investigated. The first stage is dependent upon diffusion from the surface secondary to surface agitation; this stage lasted approximately six days. The second stage depends upon internal transport and is characterized by a much slower rate of release. Both tube