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Review

The Role of Biofilms in Otitis Media with Effusion

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Abstract: The possibility of biofilms on otitis media with effusion was reviewed. A systematic literature review was conducted using PubMed, Medline, Google, and Google Scholar search engines between 1975 and 2024. Articles dealing with "otitis media with effusion", "children", "treatment", "pathophysiology", "ventilation tube", or "biofilms" were located through a search engine and retrieved through a query. A middle ear effusion, which can be either mucoid or serous and is not purulent, is a hallmark of OME. The eustachian tube disruption, age, and environmental factors have all been linked to OME. Inflammation, infection, effusion, and tissue hyperplasia are common pathways that might lead to OME, suggesting that it is a complex disorder. Whether attached to living or nonliving surfaces, biofilms comprise a collection of microbial cells surrounded by a matrix formed by the cells. This matrix accounts for about 90% of the dry mass of the biofilm. Microbiological biofilms evade both the host immune system and antibiotics. The fact that 70% of OME cultures are sterile has been known for a long time. Numerous data point to the ineffectiveness of antibiotic treatment in OME, suggesting that biofilm is responsible for the disease's chronic nature. The present high rate of further surgery can be reduced by exploring new therapeutic options made possible by comprehending the function of biofilms in the genesis of OME. The most effective way to eliminate biofilms in the middle ear is to provide antibiotics locally.

Keywords: Otitis Media with Effusion (OME); Biofilm; Ventilation Tube; Pathophysiology

1. Introduction

A middle ear effusion, which can be mucoid or serous and is not purulent, is a hallmark of otitis media with effusion (OME). While heat and headache are not typical symptoms, aural fullness or loss of hearing is. Most children with hearing loss have mild cases, and audiograms are the only way to diagnose them when the pressure in the middle ear drops too quickly compared to the outside air—a condition known as serous otitis media can develop, leading to outflow and transudate production. The character of the effusion is clear [1].

2. Methods

PubMed, Medline, Google, and Google Scholar search engines were used between 1975 and 2024 publications. The terms picked to search were "otitis media with effusion", "children", "treatment", "pathophysiology", "ventilation tube", and "biofilms" to reach all published papers on this topic.

3. Predisposing Factors for OME

Otitis media with effusion is linked to environmental factors, age, and disturbance of the eustachian tube.

3.1. Ecological Factors

Multiple epidemiological studies have demonstrated a high correlation between environmental factors, actual infections, and the heightened occurrence of otitis media with effusion. The factors contributing to this include the use of bottle feeding, feeding in a lying down position, having a sibling with ear infections, attending daycare, having allergies to common environmental substances, having a lower socioeconomic status, living in a household where people smoke, and having a family history of middle ear fluid accumulation [2].

3.2. Age

Age is a contributing factor in the occurrence of otitis media with effusion. In neonates, the eustachian tube is positioned almost parallel to the ground and gradually changes to a 45° angle, similar to adults, over several years. Furthermore, the dimensions and configuration of the eustachian tube in newborns are not conducive to the proper aeration of the middle ear [1].

Several studies in Denmark found that 24% of children's ears exhibited either type B (flat) or type C (negative pressure) tympanogram by age one. Enhancement was observed during the spring and summer, while deterioration was more prevalent in winter. Tympanograms of type B exhibited a peak in children between the ages of 2 and 4. As anticipated, due to the high occurrence of otitis media with effusion, these tympanograms declined in children older than six [1].

3.3. Eustachian Tube Dysfunction

Abnormalities in the anticipated opening of the eustachian tube in the nasopharynx are also associated with a greater incidence of otitis media with effusion. These diseases are commonly seen in adults with a cleft palate and children with Down syndrome or other abnormalities affecting the palate. Furthermore, it has been postulated that the reduced ability of the respiratory system to clear mucus and the increased thickness of mucus in individuals with cystic fibrosis may contribute to a more significant occurrence of otitis media with effusion in these patients [1].

3.4. Nutritional Regimen

According to a study conducted by Choi et al., a diet high in fat increases the likelihood of children developing otitis media with effusion. However, the efficacy of body mass index, protein, water, salt, and carbohydrate intake must be demonstrated [3].

3.5. Other Possible Factors

Unlike the Choi study, a survey conducted by Kaya et al. indicated a correlation between chronic OME and overweight or obesity in children. The study investigated weight-for-height percentiles in a group of 60 children diagnosed with chronic OME, compared to a comparison group of 86 individuals aged 2–10. The results indicated a higher prevalence of overweight and obesity in the otitis media group, suggesting that there may be a link between overweight/obesity and chronic OME, or vice versa [4].

Walker et al. [5] conducted a study that revealed preschool children with chronic otitis media with effusion exhibited symptoms such as nasal obstruction, frequent snoring, spending more hours per week in daycare, experiencing frequent colds, having siblings who had undergone tympanostomy tube placement, being born after prolonged labor, and being introduced to cow's milk at an early age. Nevertheless, individuals of Asian race and those with older siblings exhibited a decreased likelihood of developing the condition [5].

4. Pathophysiology

We need to finish the pathogenesis of OME. Inflammation, infection, effusion, and tissue hyperplasia are common pathways that might lead to OME, suggesting that it is a complex disorder. Middle ear effusion develops and persists in children due to a complex interaction between inflammation, innate immunity, mucus overproduction, viruses, bacteria, goblet cells that secrete mucus in the epithelial lining of the anteroinferior middle ear cleft, immaturity of the eustachian tube, and its relatively horizontal position [6].

The prevailing belief is that chronic inflammation, triggered by persistent bacterial remnants following an acute otitis media (AOM) episode, leads to OME. Eustachian tube dysfunction is a permanent reason for prolonged effusion in the middle ear cavity. Although myringotomy before tympanostomy tube insertion usually yields negative culture results, immunofluorescence studies and sensitive polymerase chain reaction assays reveal the presence of bacterial deoxyribonucleic acid (DNA) in the middle ear. This DNA is most commonly derived from nontypeable *Haemophilus influenzae*, indicating that bacterial biofilms also significantly contribute to the development of the condition [7–9].

Approximately 33% of middle ear effusions in newborns with OME, who undergo myringotomy and tympanostomy tube insertion, are determined to be bacterial. These cases usually lack inflammation and are primarily observed in children under two [9]. Three commonly encountered pathogens cause most AOM cases: "*Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, and *Moraxella catarrhalis.*" Research on the microbiome has revealed that the nasopharynx and middle ear fluid of children with OME are inhabited mainly by H. influenzae. While *Staphylococcus spp., Alloiococcus spp., and Turicella spp.* are common bacteria found in middle ear effusions, many more bacterial species might be involved [10].

Biofilms are crucial in the development of OME. Bacteria can survive and aggregate on the middle ear mucosa, frequently without positive bacterial cultures, because they form biofilms on pathogens. Most bacteria and viruses that attach themselves to biofilms are resistant to antibiotics. There is evidence that biofilms play a role in the development of OME. Observational studies have demonstrated the presence of bacterial DNA, messenger ribonucleic acid (RNA), and freshly formed protein in the middle ear fluid of individuals with Otitis Media with Effusion (OME).

Furthermore, biopsy samples collected from the middle ear of children undergoing tympanostomy tube installation to treat OME and recurrent AOM, but not from control children undergoing cochlear implantation, demonstrate the existence of mucosal biofilms [11, 12]. Also, tympanostomy tubes were removed from children, and tympanic membranes in children scheduled for tympanostomy tubes have been documented to contain biofilms [13]. In vitro studies indicate persistent otorrhea may be linked to biofilms that develop on tympanostomy tubes in days [14].

5. Biofilms

Microbes attach themselves to various living and nonliving surfaces and form biofilms. The biofilm's self-produced matrix can comprise over 90% of its dry mass [15, 16]. Aside from exopolysaccharides, the dried matrix contains lipids, proteins, RNA, DNA, and biological components [16]. One way of looking at biofilms is as a way for microbes to develop in a protected habitat.

There are typically five phases to the creation of biofilms [17]. Planktonic cells reversibly adhere to surfaces using "flagella, pili, fimbriae, and polysaccharide adhesions." However, as microbial cells proliferate, their attachment becomes more substantial and eventually irreversible because of the extracellular matrix polysaccharides and proteins they produce. As these cells grow in number, they start to secrete more matrix and eventually form small clusters of cells called microcolonies. As these microcolonies expand, they merge into larger microcolonies, a fully developed biofilm structure. Finally, cells can either disperse from microcolonies to form a new biofilm or increase in size to a condition like a planktonic cell.

Biofilms are complex three-dimensional formations consisting of microbial cells and their extracellular matrix. Inside these structures, groups of microbial cells are divided by open water channels. These channels act as a basic circulatory system, carrying oxygen and nutrients and removing waste products from metabolism. Nutrient, waste product, and secreted signaling compound chemical concentration gradients are established within the biofilm strata due to the architecture above's functionalities. It is essential to mention that these gradients have the potential to cross or overlap, resulting in the formation of many different microenvironments inside microbial

biofilms [18]. In order to adapt to specific spatial positions within biofilms, microbial cells exhibit characteristic patterns of gene expression and cell physiology [15, 18].

5.1. Biofilm Associated Infections

Infections resulting from biofilms may be classified into two primary categories: those associated with implanted medical devices and those that impact host tissues [19, 20]. In the former situation, infectious biofilms develop on the surfaces of medical devices inserted into the body. The listed devices include urine catheters, central venous catheters, mechanical heart valves, joint prostheses, cardiac pacemakers, endotracheal tubes, contact lenses, intrauterine devices, waterlines from dental units, cerebrospinal fluid shunts, and cardiac pacemakers. During these occurrences, pathogenic biofilms may form on the surfaces of implanted medical devices, facilitating the entry of pathogens into human organs or tissues through these devices [19]. These infections might come from the normal bacteria found on the skin or mucous membranes of patients, healthcare staff, or the environment. Chronic otitis media, native valve infectious endocarditis, chronic prostatitis, chronic rhinosinusitis, chronic wounds, recurrent urinary tract infections, periodontitis, dental caries, and cystic fibrosis are among the prevalent chronic opportunistic infections linked to biofilms in humans.

Interactions between many species can increase the duration of biofilm-associated illnesses, but they can be generated by a single species or a combination of species. Fungi (particularly *Aspergillus spp. and Candida spp*.), Gram-negative bacteria (particularly *Pseudomonas aeruginosa, Escherichia coli, and Klebsiella pneumoniae*), and Gram-positive bacteria (particularly *streptococci and staphylococci*) are common pathogens implicated in biofilm-associated illnesses. The bacterial pathogen *Pseudomonas aeruginosa* and the fungal pathogen Candida albicans will be mentioned several times in this study. Among the most common causes of healthcare-associated infections, *Candida albicans* contaminates indwelling medical equipment and induces superficial and deep systemic disorders [21, 22]. In immunocompromised hosts, such as those with cystic fibrosis, *Pseudomonas aeruginosa* can induce local acute and chronic lung infections, which can lead to severe complications and even death.

The considerable antibiotic resistance among biofilm-growing bacteria makes it difficult to treat infections caused by biofilms effectively. Because traditional antibiotic treatment methods like antibiotic prophylaxis, early aggressive antibiotic therapy, and chronic suppressive antibiotic therapy fail to eradicate all microbial cells in a biofilm—particularly those located in the film's core—biofilm-associated infections tend to be recurrent and long-lasting.

5.1.1. Enzymes with Antimicrobial Activity

The innate immune systems of plants and animals, as well as bacteria and fungi, create antimicrobial peptides (AMPs), which are cationic, amphipathic peptides ranging in length from fifteen to thirty amino acids. Bacteria are less likely to acquire resistance when AMPs attach to negatively charged structural molecules on their membrane. These AMPs have a wide range of antimicrobial effects. Since this is the case with biofilms, they effectively target sluggish bacteria to develop or not grow at all [23, 24].

As AMPs may have their primary amino acid sequences tweaked to make them more stable and practical, they serve as excellent building blocks for creating new anti-infectious medicines. Synthetic, modified AMPs have recently gained popularity as an antibiofilm technique due to their inexpensive production costs in higher numbers [24, 25]. Proteolytic activity in bodily fluids, pH, and physiological salt concentrations pose problems for the therapeutic use of AMPs [15].

5.1.2. Enzymes that Break Down Biofilm Matrix

An effective strategy for decreasing biofilms involves using enzymes that degrade the biofilm matrix. These enzymes comprise DNase I, which hydrolyzes extracellular DNA, and α-amylase and DspB, which degrade extracellular polysaccharides. Both natural and recombinant forms of human DNase I can destroy the biofilms of various bacteria and fungi crucial in medical care [26, 27]. The addition of DNase I enhances the efficacy of antibiotics by modifying the structure of the biofilm through the breakdown of extracellular DNA. This modification facilitates a greater penetration of antibiotics into the biofilm. Studies have shown that α-amylase can inhibit the formation of biofilms and successfully degrade established biofilms of S. aureus, Vibrio cholerae, and P. aeruginosa [28, 29]. DspB, derived initially from *Actinobacillus actinomycetemcomitans*, is a soluble β-N-acetylglucosaminidase that exhibits many ca-

pabilities, such as the ability to degrade the matrix exopolysaccharide present in bacterial biofilms. Combining DspB with antibiotics, disinfectants, or surfactants demonstrates a synergistic effect on bacterial pathogens like *Acinetobacter baumannii*, Staphylococcus epidermidis, and Staphylococcus aureus [30, 31]. This reduces bacterial colonization on medical devices and prolongs superior antimicrobial and antibiofilm activity.

5.1.3. Bacteriophages

The use of bacteriophages, which are essentially bacterial parasites, as a means of combating bacterial illnesses dates back many decades [32]. There are three reasons why bacteriophages can undermine biofilm protection: first, the phage replicates in the host cells of infected bacteria; second, the lytic cycle produces and releases "progeny phages" in high quantity; and third, lysis of radial cells happens in the vicinity of infection sites [33]. Phage offspring can spread radially inside a biofilm [34]. In theory, biofilm-associated infections can be treated with a single dosage of phage [15, 35].

5.1.4. Ultrasound Therapy

Chronic rhinosinusitis is an immune ailment influenced by environmental variables, microbial biofilms, and immunological diseases; for a long time, low-frequency ultrasound was recommended as a treatment for this condition [36]. Combining low-frequency ultrasound with antibiotics shows promise for biofilm removal. However, low-frequency ultrasound is inefficient in killing bacteria forming in biofilms [37]. Because therapeutic ultrasound physically breaks down compact biofilm barriers and increases antibiotic uptake by making bacterial cell membranes more permeable, it can cause bacteria that grow in biofilms to be more sensitive to antibiotics [15, 36].

5.2. Biofilms and OME

It has long been known that seventy percent of the cultures in OME are sterile. Numerous findings point to the fact that antibiotic treatment does not affect OME, suggesting that biofilm is the agent responsible for the chronic character of the disease [38, 39].

Bacteria commonly reside in stationary populations and are known as biofilms [40]. These communities have morphological and physiological characteristics distinct from free-living bacteria, making them more resilient to external influences [40]. A consistent observation in pharmacokinetic drug penetration investigations is that the bactericidal concentration of the treatment may be readily achieved in the ear. Additionally, investigations on planktonic bacteria have shown that they are sensitive to antibacterial drugs when tested in vitro. The mucosal biofilm theory also explains why tympanostomy combined with ear draining is the most effective therapy for other types of otitis media. A habitat conducive to forming a bacterial mucosal biofilm is within the middle ear, which has inadequate ventilation. Because of the following factors, ventilation tube surgery is a technique that is considered to be effective:

1. The restoration of ventilation in the middle ear raises the oxygen concentration in this region, which has the potential to alter the phenotype of the biofilm;
2. The mechanical removal of exudate after cutting the tympanic membrane interrupts the flow, purifies, and decreases the size of the biofilm.
3. Restoring ventilation facilitates the reconstruction of the host's defense systems in the mucosa of the middle ear. These alterations lead to the refinement of biofilm and the termination of exudate [41].

The OME etiology model describes a chronic middle ear effusion caused by pathogenic bacteria creating biofilm on the mucosa of the middle ear. Instead of being an aseptic inflammatory process, this idea proposes that OME is an active chronic bacterial illness to be more accurate. Because biofilm was discovered on the mucous membrane of the middle ear of the chinchilla in otitis media that was experimentally caused by *Haemophilus influenzae* [42], the findings of experimental research support this notion.

This clinical observation that ventilation drainage is the most successful means of treating OME is congruent with the biofilm theory, which is also consistent with the clinical observations. Since past viral infections and chronic hypoxia affect the typical defensive mechanisms of the mucosal membrane, the middle ear, which is not ventilated, is an excellent habitat for biofilm creation. The mucosa of the middle ear, which is in good condition, is made up of

ciliated epithelial cells that are engaged in the processes that purify bacterial cells. OME is characterized by a lack of cilia in the epithelium of the middle ear while simultaneously exhibiting an abundance of secretory cells, and the number of these cells rises throughout OME. In addition to restoring ventilation of the middle ear, the placement of the tympanostomy tube results in a rise in the partial pressure of oxygen, which in turn induces a change in the phenotype of the organic biofilm. The removal of exudate by suction causes the biofilm to be broken up and reduced in bulk; it raises the oxygen level and results in the regeneration of the ciliary epithelium [43].

The illness known as otitis media with effusion is characterized by a persistent inflammation that affects the mucosa of the middle ear. This condition leads to the accumulation of mucus discharge in the middle ear cleft [44]. An altered phenotype in terms of growth rate and gene transcription is exhibited by biofilms, which are structured communities of bacteria that are embedded in a self-produced extracellular matrix and attached to a surface or interface that may be surrounding mucus or fluid. Biofilms have the potential to cause a low-grade inflammatory reaction, which may then lead to the development of clinical symptoms of OM [45].

Because of their naturally poor resistance to antibiotic treatment, bacterial biofilms are notoriously difficult to remove with standard antibiotic therapy. To destroy them, it is often necessary to reach antibiotic concentrations that are ten to one thousand times greater than those required to inhibit planktonic bacteria [45]. Recalcitrance, a diminished sensitivity to antibiotics, is a characteristic separate from antibiotic resistance caused by genetic mutations. Since biofilms are less sensitive to antibiotics, it is challenging to achieve antibiotic concentrations in the middle ear that are adequately high. Additionally, the failure of oral antibiotics to have any persistent therapeutic effect in OME may be attributed to concentrations that are too low [46].

Bacterial biofilms may form on tubes coated with polyvinylpyrrolidone or treated with silver oxide. Nevertheless, ion-bombarded silicone and phosphorylcholine-coated fluoroplastic tubes resist biofilm development by Staphylococcus aureus and Pseudomonas aeruginosa [47].

6. Conclusions

After understanding the role of biofilm in the pathogenesis of OME, prospective novel therapy routes can be explored to lower the high rate of further surgical procedures [45]. The most obvious alternative is to administer the antibiotics locally to attain antibiotic levels in the middle ear that are high enough to eliminate biofilms. Since biofilm elimination takes treatment for several weeks, a formulation with modified release capability would be necessary. It is possible to put this modified-release device into the middle ear and the initial VT. It would then release antibiotics for many weeks, and subsequently, it would undergo decay without the need for mechanical removal [44].

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Conflicts of Interest

The authors declare no conflict of interest.

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