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A Review

Chronic Tonsillitis and Biofilms: A Brief Overview of Treatment Modalities

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Review Article

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Abstract

Recurrent tonsillitis is described as when an individual suffers from several attacks of tonsillitis per year. Chronic and recurrent tonsillitis both cause repeated occurrences of inflamed tonsils which have a significant impact on a patients' quality of life. Numerous children suffer from recurrent tonsillitis, and sore throats and these illnesses become part of their life. Antimicrobials can provide temporary relief, but in many cases, tonsillitis recurs. Scientists working at Washington University School of Medicine in St. Louis identified the cause of such recurrent infections as microorganisms which often create biofilms and a repository of infection in the wet and warm folds of the tonsils. This review will discuss different treatment modalities, their advantages and disadvantages and new treatment options focusing on biofilms. All treatment options should be selected based on evidence and individual need.

Tonsillitis

Tonsillitis is an inflammation of the pharyngeal tonsils. The inflammation may affect other areas of the back of the throat, including the adenoids and the lingual tonsils. Acute tonsillitis is an infection of the tonsils triggered by one of several types of bacteria or viruses and peritonsillar abscesses can also occur. Chronic tonsillitis is a tenacious infection of the tonsils which may result in tonsil stones. Recurrent tonsillitis ensues when an individual suffers from several incidents of tonsillitis per year. Both chronic and recurrent tonsillitis involve repeated occurrences of inflamed tonsils which can impact severely on a patients' quality of life. [1, 2] Children very often suffer from tonsillitis although it is seldom observed below the age of 2 years. Tonsillitis due to Streptococcus bacteria classically happens in children aged between 5-15 years, while viral tonsillitis is more prevalent in younger children. [3] Multiple studies report that the average prevalence of carrier status of school children for group A Streptococcus is 15.9%. [4, 5]

Epidemiology of Tonsillitis

Numerous children so often suffer from recurrent tonsillitis and sore throats that these illnesses become their part of life. For example, one study indicates that approximately 30% of peritonsillar abscesses require a tonsillectomy [6] and another indicates that recurrent tonsillitis is reported in 11.7% and 12.1% of Norwegian and Turkish children respectively. [7] Many of these patients are prescribed antimicrobials which typically provide temporary relief, but then the tonsillitis recurs. [8] Scientists working at Washington University School of Medicine in St. Louis identified that recurrent infections are exacerbated by the creation of biofilms in the wet and warm folds of the tonsils by microorganisms which act as a repository of infection. [9] A study utilizing an innovative imagining technique in single sections of human mucosal tissue reports the presence of biofilms in 70.8% chronic tonsillitis patients. [10] Another study revealed that biofilms were recognized on the surface epithelium of tonsils and adenoids in many of the patients who were waiting for adenotonsillectomy due to chronic tonsillitis and adenoiditis. [11] Such biofilms are also observed in other otorhinolaryngology related infections such as chronic rhinosinusitis and chronic otitis media with effusion. [12, 13]

A Brief Overview Regarding Biofilms

Biofilms are systematized communities of microorganisms embedded in a hydrated matrix of extracellular polymeric substances causing diverse of persistent infections, including dental plaque, cystic fibrosis, urinary tract infections, osteomyelitis, and ear infections. [9, 14, 15] Biofilm formations is a prehistoric prokaryotic strategy of a microorganism to exist and grow in antagonistic settings through building innovative communities through several processes. [16-19] The Dutch scientist (commonly known as the Father of Microbiology) Antonie van Leeuwenhoek used his primitive but effective microscope to observed Biofilms as early as 1674 and describes aggregates of animalcules scraped from human tooth surfaces. [20, 21] The English phrase *'survival of the fittest'* arose from Darwinian evolutionary theory and describes one of the mechanisms of natural selection. [22, 23] Bacterial biofilm formations are a form of 'survival of the fittest' under adverse conditions including chemical or antimicrobial treatment. [24, 25] The formation of biofilms by bacteria has four potential advantages: "i. *Protection from harmful conditions in the host*, ii. *Sequestration to a nutrient-rich area*, iii. *Utilization of cooperative*

Biofilms normally grow as biofilms and planktonic cultures are an in vitro artifact". [26] Microbial biofilms were identified as a major cause of many human infections, present in more than 65-80% of all human bacterial infections. [14, 27-30] Thereafter biofilm pose *"a serious problem for public health because of the increased resistance of biofilm-associated organisms to antimicrobial agents and the potential for these organisms to cause infections in patients with indwelling medical devices*". [31] Biofilm formations is generally considered to arise in four core stages: (1) bacterial attachment to a surface, (2) microcolony formation, (3) biofilm maturation and (4) detachment (also called dispersal) of bacteria which may then colonize new areas. [32] Multiple research reported that the process of biofilm formation is categorized by five stages. [33-35] (1) Microbial cells attach to surfaces reversibly. [36] (2) Microbial cells then attach to surfaces irreversibly. [37] (3) Cells adsorbed on surfaces and grow into microcolonies, their physical dimensions estimated tens or hundreds of microns in diameter. [38] (4) There microbial fraternity grows into a three-dimensional configuration and settle down into a biofilm as cells replicate and the extracellular polymeric substances (EPS) accumulates. [39] (5) Bacterial cells detach biofilm and disperse into the bulk fluid, where they act free swimming bacteria or and form new biofilms. [16, 17] Biofilm formations were depicted in Figure 1 and 2.

Distinct Features of Biofilm Bacteria

Bacteria found inside biofilms have distinct features different from those of free-swimming (planktonic) bacteria of the same classes and possess a very high level of resistance to commonly-used antimicrobial remedies, biocides and antiseptics, and the host immune response. [40-42] Older, mature and impenetrable biofilms are consistently more resistant to antimicrobials than younger, less dense biofilms. [42] Bacterial cells residing in the outermost parts of the biofilm are more vulnerable to the host's defenses and antimicrobials, although these microorganisms possess numerous defensive mechanisms. The biofilm is formed of various microbial communities that create a complex three-dimensional physical barrier which hinders the diffusional penetration of antimicrobials. [17, 43, 44] The exterior layer of biofilm metabolic activity alters the local pH to be more acidic and creates anoxic zones that help to degrade antimicrobials. [45-48] The biofilm also creates nutrient-depleted areas which act on microbes to put them into a stationary or dormant phase, which may also contribute towards antibiotic resistance. [49, 50] The extracellular matrix of the biofilm secretes polymers that bind and deactivate antimicrobials, forming an antibiotic "*sink*". [51] These properties of biofilms (inadequate diffusion of nutrients, restricted antimicrobial transmission and the alteration of the environment to produce a more hostile environment) combine to produce a widespread resistance and tolerance to antimicrobials. [16, 43-56] In addition, microbes entrenched in a biofilm can exist even in high concentrations of bactericidal antimicrobials although they are abundantly sensitive to those antimicrobials in culture plates under planktonic conditions. [57] This complex phenomenon is known as the *"recalcitrance of biofilm bacteria toward antibiotics"* [58] and microorganisms found in biofilms can be up to 500-1,000 times more tolerant to antibacterial compounds than their planktonic counterparts. [59-62] Additionally, many studies reported that as soon as a biofilm is rooted and fixed, microbes develop resistance to several categories of physicochemical aggression, including UV light, heavy metals, low pH, changes in hydration or salinity, and phagocytosis. [63-67]

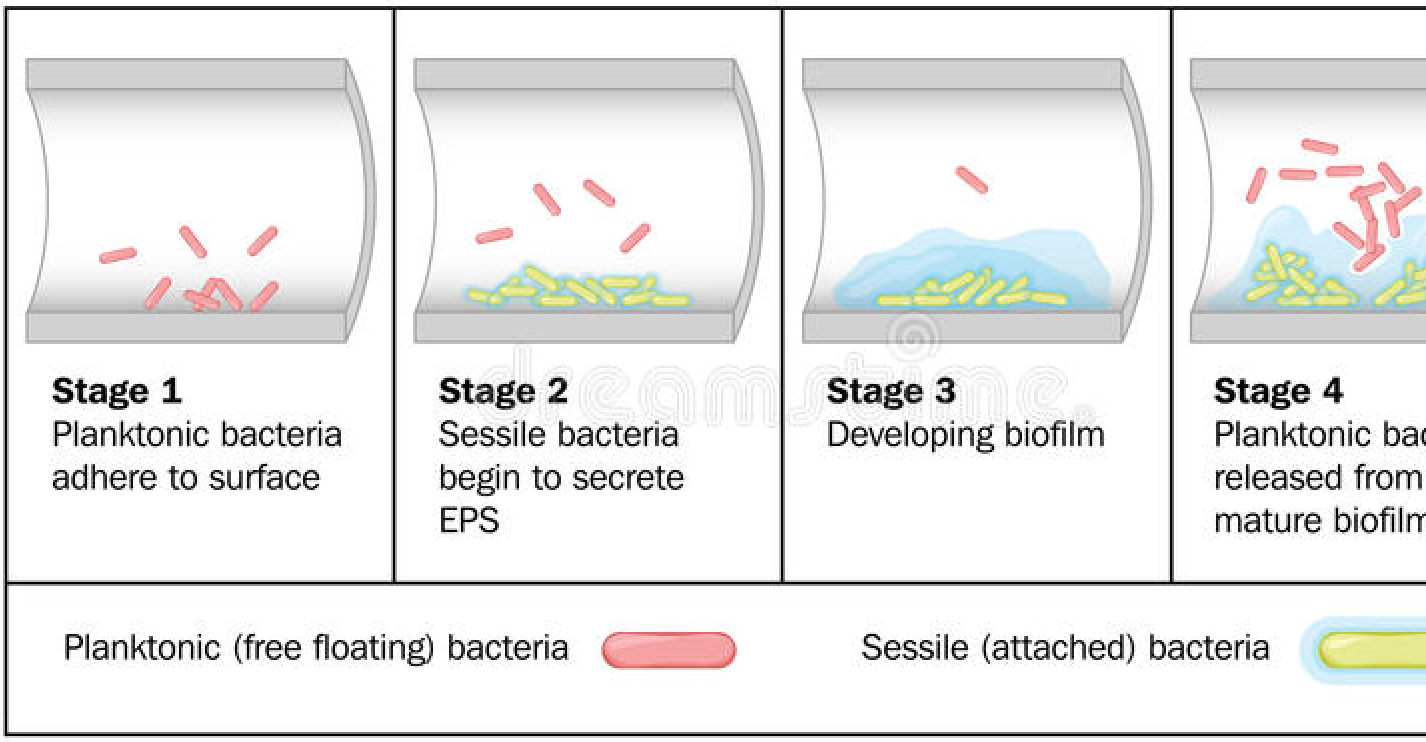

Figure 1: Showing Four Different Stages of Biofilm Development. Image was download from images for c
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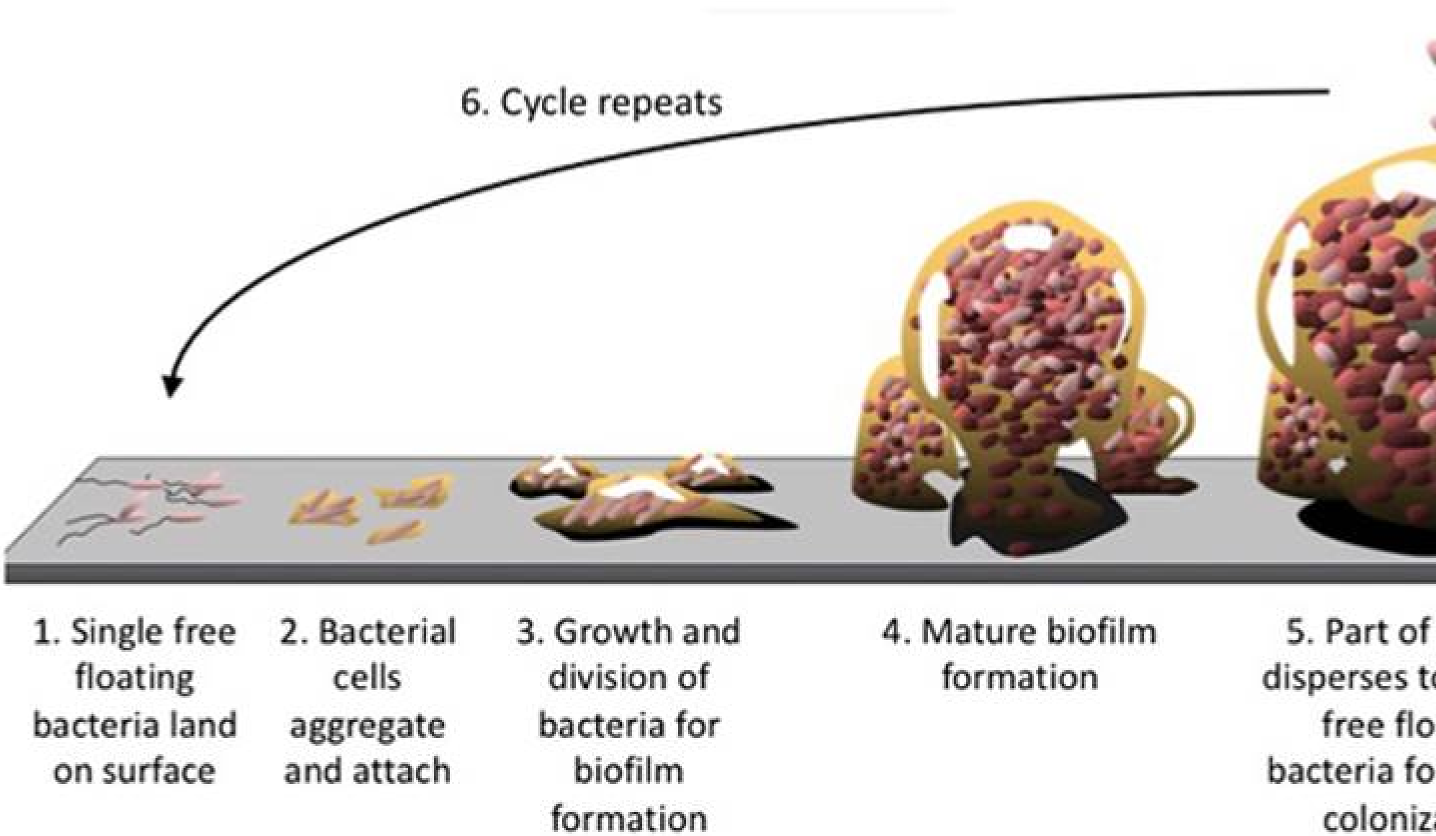

Figure 2: Showing Five Stages of Biofilm Development. Image was download from images for copyright fre
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Recurrent Tonsillitis and Tonsillectomy

Chronic tonsillitis affecting equally both children and adults is a serious health problem [68, 69] and whilst the definition of severe recurrent tonsillitis varies, a quantity of severity is described as five or more episodes of true tonsillitis a year, symptoms for at least a year, and episodes that are disabling and prevent normal functioning. [70, 71] In one study, the lifetime prevalence of recurrent tonsillitis is described as 11.7% (95% confidence interval, 11.0%-12.3%) with a significant preponderance of females. [7] Recurrent tonsillitis is typically treated by either surgery or, when the patient does not meet tonsillectomy benchmarks or there are surgical or medical contraindications, by medical antimicrobial intervention. [72, 73]

Whilst tonsillectomy (surgical removal of the tonsils, with or without adenoidectomy) as a treatment modality has been practiced for over 100 years for children, much controversy exists around its value. As for example, in 1951 the British Medical Journal reported that "*it is better to delay a decision than to hurry it, and above all to avoid operating on tonsils which have been recently inflamed*". [74] One study suggests that 0.6 episodes of any type of a sore throat were reported in the first year after surgery compared to medical intervention [75] and another reported that surgery could lead to life-threatening complications. A Swedish cohort study reports that among post-tonsillectomy patients 20 years later, there was a higher incidence of *"chronic, immune-mediated diseases … in the operated group",* with a statistically significant relationship between post-tonsillectomy and chronic disease, with a relative risk at 9.41 and a confidence interval from 1 ($1.13 < RR < 78.14$). [76] However, another research study focusing on adults found that tonsillectomy promotes and improves long-term health and quality of life, thus saving health resources. [77]

The decision to operate should therefore be taken with care based on an individual patient's needs and history, plus current research evidence. [74, 76, 78, 79] In making such decisions, secondary care doctors and family medicine practitioners need to collaborate because the decision whether a tonsillectomy is necessary is quite difficult and both the GP and the otolaryngologist must contribute equally. [74] The GP knows about the patient's frequency, duration and severity of tonsillitis whereas the ENT specialist will evaluate symptoms relating to nasal and Eustachian impediment, and will assess whether symptoms are due to tonsillitis or chronic sinusitis. [74]

Treatments Aimed at Disrupting Biofilms

Microbial biofilm formation is responsible for the development of acute to chronic infection in several diseases including cystic fibrosis; periodontitis; infective endocarditis; persistent otitis media; chronic rhinosinusitis; chronic tonsillitis; prostatitis; chronic osteomyelitis; atopic dermatitis; onychomycosis; dental caries; infectious kidney stones; and chronic wounds. [80-83] As well, biofilms formed on the any surface, living or non-living, even on clinical devices like pacemakers, implants and catheters, and very difficult to eradicate, which accentuates the clinical consequence, such as Pseudomonal infections can embroil any part of the human body. Further, the micro-organisms adaptive capability and genetic ups and downs of within the biofilm transform them resistant to all known antimicrobial medicines. Thereafter the Pseudomonal infections become real critical to be handle by the medical doctors and threatens human life. [83, 84] By and large it is thought that 99% of the biosphere's bacteria to live in biofilms. Thereafter, it is believed that microbial community gain an advantage living in this state. [85] Consequently, microbial biofilms significantly affecting human health by increasing morbidity, mortality, and healthcare cost. Biofilm not only adding to hospital-acquired infections (HAIs) by increasing chronicity and persistence, but colonizing in other areas of environment instigating corrosion, fouling of water pipes, and food and pharmaceutical decomposition.[14, 86-88] Another study reported microbial biofilm can stick and infect all medical devices such as orthopedic prostheses and intravascular catheters and promote up to 60% of HAIs. [89]

Microorganisms in biofilms are distinctively more resistant to antimicrobial agents and environmental insults and are therefore very difficult to eradicate. [42, 90-94] Biofilms in general (and chronic tonsillitis specifically) can therefore lead to substantial economic costs for countries and individuals, health concerns and an evolving public health problem in both high and low resource settings. [77, 95-100] Because of this, multiple research studies have attempted to resolve the issues of both biofilms and recurrent tonsillitis. [59, 61, 101-108]

The explosion of antibiotic resistance throughout the world of many microbial strains has put pressure on the research and medical communities to find an alternative strategy for the management of biofilm-mediated diseases. [61] "*Perhaps new antibiotics are not the only way to combat biofilm infections if we could make ineffective older antibiotics active again*." [59] This researcher developed a 2-amino-imidazoles molecule which is capable of disrupting biofilms through making a microorganism which was previously antibiotic-resistant more vulnerable to older antimicrobials. [59, 62] Immunotherapy (using cyclic di-nucleotides) has been effective in the management of different cancers, and this molecule has also been utilized as a therapeutic strategy for biofilm-related infections. Immunoprophylaxis and immunotherapy might therefore provide new tools to combat S. epidermidis biofilm formation. [109, 110] Recently, multiple studies revealed that a 3,5-cyclic diguanylic acid (c-di-GMP) binding protein was found in biofilm communities. [111, 112] BdcA (a protein that enhances biofilm dispersal), confiscates c-di-GMP and minimizes its local concentration and is partly responsible for the reduction and down-regulation of EPS of biofilms and for the up-regulation of swimming, swarming, and planktonic microbes. [111, 112] This phenomenon has been observed in Pseudomonas species and the Rhizobium mellioti biofilm communities. [111, 112] Multiple group of scientists recently reported that CdrA (an adhesin compound) which is produced by biofilms in response to high levels of c-di-GMP that binds with Psl and stabilizes biofilm structure. [38, 106, 113] Multiple research studies have identified at least three extracellular polysaccharides (Alginate, Pel and Psl) that have been important implication in structure maintenance and antibiotic resistance of biofilm. [114-123] Another study revealed that exogenous addition of D-amino acids [109] disrupted preformed biofilms by disturbing adhesive fiber interactions and was also effective in preventing biofilm formation by S. aureus and P. aeruginosa. [124-126] One-more biofilm-disassembly molecule is norspermidine which has a similar dispersal mechanism to D-amino acids by targeting the exopolysaccharides. [125] The biofilm-inhibiting properties of norspermidine were detected in Staphylococcus Aureus and Escherichia coli pellicle biofilm.[125] Current research therefore needs to focus on the development of norspermidine, BdcA, D-amino acids, and other polyamines as a novel antibiofilm approach and medical communities should no longer depend exclusively on antimicrobials (which are increasingly ineffective with many pathogenic microorganisms because of resistance) and surgery to treat infectious diseases. [104, 111, 112, 124, 125]

Other studies have identified additional ways of disrupting biofilms. Bioactive enzymes such as dispersin or Proteinase K studied in orthopedic implants made bacteria more susceptible to antibiotics and finally eradicated the biofilm by affecting polymers or proteins of the biofilm structure. [127] Several cytotoxic agents have also been found to successfully eliminate biofilms from implant surfaces, with citric acid being reported to be the most successful in eradicating biofilms on titanium surfaces. [128] Multiple research studies have identified that an electrical current successfully detaches Staphylococcus aureus and Staphylococcus epidermis biofilms from stainless steel implants. [129-131] Another study observed that biofilms of Staphylococcus epidermis on stainless steel fasteners were successfully eradicated through pulsed electromagnetic fields in combination with gentamicin. [132] A new cluster of research studies have used laser-generated shockwaves to effectively break up biofilms. [133] The technique is founded on a Q-switched, ND: YAG rhythmically laser functioning at a "*rep rate of 10 Hz with 1500 mJ pulses centered at 1064 nm. The laser pulses were used to create shockwave pulses in Al coated polycarbonate substrates and a resulting peak stress of greater than 50 MPa*" was able to reduce 55% living microorganisms. [134] The laser technique offers another way of disrupting biofilms and is useful in the management of infected wounds, where standard treatment modalities such as topical antimicrobials or the removal of dead, damaged, or infected tissue is unsuccessful or injurious. One study found that just 4-10 seconds of the laser therapy was able to disperse biofilms from nitinol stents on 97.9% of Pseudomonas aeruginosa to single-celled planktonic microorganisms that can be more easily treated with antibiotics. [135] Another found that laser-generated shockwaves therapy quickly disrupts the biofilms in infected wounds to eliminate the microorganisms and intensify the effectiveness of topical antimicrobials in the residual biofilm. Such interventions will promote patients' quality of life by reducing healing times, morbidity, and save healthcare costs. [136]

N-Acetyl-Cysteine (NAC) is an antioxidant mediator which reduces the variety of microbial bacteria on biofilm emergence and evolution, [137] inhibits the manufacturing of the extracellular polysaccharide matrix [138] and promotes the disruption of mature biofilms. [133] NAC has been found to reduce Streptococcus pneumoniae and Haemophilus influenzae adhesion to human oropharyngeal epithelial cells in laboratory experiments. [138] Chronic infections raise prostaglandin levels and NAC effectively reduces these levels and helps to disrupt the biofilms. [139-142] correspondingly, aspirin-like non-steroidal anti-inflammatory drugs (NSAIDs) decrease biofilm production and completely block fungal infections. [143] NAC interacts with the sulfhydryl group of enzymes involved in EPS production or excretion, which reduces the activity of these molecules or inhibits cysteine utilization. [144] NAC therefore, decreases in-vitro biofilm formation [145] and research on salicylates shows a similar negative effect on the production of biofilm. [146] A study which applied both found that therapeutic doses of acetylsalicylic acid (ASA) and NAC diminishes tonsillar mucosal biofilm formation in chronic or recurrent tonsillitis. [102] An Iraqi study found a strong correlation between the biofilm of Streptococcus pyogenes and recurrent tonsillitis and that three types of vinegar eradicated streptococcal biofilm remarkably: Date (100%), Apple (95.5%), and Grape (90.9%). [105] A later study also demonstrated the potential of vinegar in eradicating tonsillar biofilm. [101] In a laboratory experiment, whilst washing and cleaning with a soft brush did not remove the chronic tonsillitis biofilm layer on the tonsil surface in, using a harder brush removed more biofilm. [103] Researchers believe that the physical removal of biofilm (by brushing or using ultrasound-activated bubbles) from the tonsil surface in vivo will lead to greater effectiveness of topical antimicrobials and decrease the need for systemic antimicrobials. [103]

Conclusion

Recurrent or chronic tonsillitis is currently a global public health issue which can severely impair an individuals' quality of life. [77, 147] Microbial biofilms are a major cause of repeated tonsillitis in both pediatric and adult cohorts and more research is needed to develop new treatment strategies. [107,148, 149] Treatment modalities should however be based on careful selection and individual consideration of the potential impact of biofilms on cases of recurrent tonsillitis. [74] Rather than developing or using more potent antimicrobials, doctors should ensure they are up-to-date with research and the treatment of biofilms, including the application of topical agents, the physical removal of biofilms and other innovative treatments.

Conflict of Interest

Authors declare no conflict of Interest.

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