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BACTERIAL BIOFILMS IN CHRONIC RHINOSINUSITIS. CLINICAL ROLE AND CURRENT THERAPEUTIC STRATEGIES

Biofilms, sophisticated microbial communities on both living and inert surfaces or in loose aggregates, present a formidable structure through an intercellular matrix. This configuration not only enables microbes to thrive under harsh conditions but also enhances their resistance against antimicrobial treatments. Emerging research underscores the pivotal role of biofilms in the progression and persistence of chronic infections, notably chronic rhinosinusitis (CRS). Historically, the significance of biofilms in CRS was underappreciated, but recent breakthroughs in detection techniques and molecular science have illuminated their substantial influence on this condition. This revelation has positioned the study of bacterial biofilms at the forefront of otolaryngology, especially in tackling stubborn cases of CRS. This paper delves into the latest insights on the clinical impact of biofilms in CRS, offering a comprehensive review of both existing and innovative treatment approaches aimed at eradicating biofilm-associated complications. Through this exploration, the paper aims to foster further research and development of effective strategies for combating biofilm-associated CRS among the scientific and medical community. In particular, attention is paid to alternative antimicrobial agents, such as bacteriophages, nanomaterials, and antimicrobial peptides. The perspective of applying anti-matrix and anti-adhesive methods is revealed. Also, as one of the promising directions for combating biofilms, methods of influence and disruption of cellular quorum sensing are presented.

***Keywords**: bacterial biofilms, chronic rhinosinusitis, biofilms elimination, antimicrobial drugs, cell quorum-sensing.*

As known, the existence of bacteria goes through two possible forms — planktonic and biofilm. The form of biofilm is a way more preferable for bacteria to exist as it opens the possibility to build a reliable and resistant to outer risks community of bacteria, which, despite the slow growth and development, can provide more chances for long-term survival.

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Biofilms are a complex aggregation of microorganisms that form on biological and non-biological surfaces, forming a strong structure owing to the intercellular matrix. In contrast to the planktonic form of existence, the biofilm form enables microorganisms to survive in much more adverse conditions and more effectively develop resistance to antimicrobial drugs (Fastenberg et al., 2019).

The process of biofilm development is based on planktonic bacteria primary adhesion to the biological surface with the following development stages: attachment, microcolony formation, maturation, and expansion on the nearby tissues. After the process of expansion is initiated, biofilm starts to release separate planktonic bacteria, which float to the sites of the host tissues. Meanwhile, planktonic bacterial units are endowed with transcribed DNA, which exhibits characteristics of the colony — the process of DNA transcription occurs while maturation due to increasing synthesis of signaling molecules and alterations in intercellular signaling. Described processes are regulated by mechanism of quorum-sensing (QS) — an ability of bacteria to communicate through the colony using the system of signaling molecules, which are called autoinducers (Fastenberg et al., 2019).

Combination of a variety of adaptive mechanisms give an opportunity for bioflims to develop antimicrobial resistance in different ways, such as a physical barrier (due to the extracellular matrix), enzymatic activation, and stacked organization of biofilm, which leads to the development of «persister cells» — bacteria which lie in deep interior of biofilm and have significantly reduced metabolic activity, so this leads to much less nutrient consumption. Also, «persister cells» endure a higher concentration of antibiotics and promote infection with the same resistance phenotype to the other sides of host tissues (Fastenberg et al., 2019).

In recent years, there have been increasing evidences in the literature that biofilms play an important role in the pathophysiology of chronic inflammative infections in otolaryngology. Such common pathologies like chronic tonsillitis, chronic otitis media with effusion, and cholestetoma are known to be induced by biofilms, so is chronic rhinosinusitis (CRS) (Ramakrishnan et al., 2015). Until recently, the understanding of the role of biofilms in pathophysiology of CRS was quite limited, as biofilms were indicated at healthy individuals as well. Last years advances in biofilm identification methods and molecular biology have shed new light on the role of biofilms in CRS. Studies of species diversity of biofilms were performed in patients with CRS — *Staphylococcus aureus*, couagulase-negative staphylococcus (CNS), and *Pseudomonas aeruginosa* were the most frequent bacteria isolated with the *S. aureus* leading in occurrence. However, Gram-negative rods, particularly *P. aeruginosa*, take a substantial role in CRS recalcitrance. Also, there is some controversy about classical non-pathogenic species, which are commonly found in patients with CRS — especially couagulase-negative staphylococcus (*S. epidermidis)*. Despite of being found on the nasal mucosa of majority of healthy individuals, it can perform pathogenic activity due to the phenotypic difference between truly pathologic CNS in CRS and CNS in healthy individuals found as a contaminant (Larson et al., 2011).

It is known that the presence of biofilms in CRS significantly complicates the course of the CRS and prolongs the duration of treatment. Biofilms act as a strategy for bacteria to persistently infect the sinuses without directly invading the tissues, and superantigens could play a role in facilitating the inflammation associated with this process. Considering this, the biofilms research programs gain its relevance making the priority of the search for new therapeutic strategies that will make it possible to destroy the structure or completely destroy biofilms in patients with CRS (Ramakrishnan et al,. 2015).

Aim. This review aims at assessing the clinical significance of the impact of biofilms on the course of CRS, considerimg potential therapeutic strategies to combat biofilms in CRS, and highlighting future research directions in the search for effective anti-biofilm therapeutic strategies.

Clinical role of biofilms in CRS. Bacterial biofilms are probably one of the key factors of the severe course of CRS. In 2006, the original research showed up the correlation between the presence of *P. aeruginosa* and *S. aureus* biofilms in CRS patients and poor results of surgical treatment of CRS (Bendouah et al., 2006). Prince et al. showed that patients with recalcitrant CRS were more likely to be affected by biofilm-forming bacteria after functional endoscopic sinus surgery (FESS) (Prince et al., 2008). Psaltis et al. demonstrated that patients with CRS with bacterial biofilms had worse preoperative computed tomography (CT) findings of the paranasal sinuses and, on average, after 8 months of follow-up, these patients had longer postoperative reactive inflammatory sings of the nasal cavity and paranasal sinuses compared to patients without biofilms (Psaltis et al., 2008). A subsequent prospective study confirmed these findings by using subjective and objective data, and also showed that patients with biofilms had a statistically higher number of complaints of sinus discomfort and required repeated postoperative visits and repeated antibiotic treatment (Shaghayegh et al., 2022). This conclusion needs further confirmation, as such results have been variously replicated in other studies (Huang et al., 2022).

Some studies have shown that certain types of biofilms (dominant-type *S. aureus* biofilms, single-type *Haemophilus influenzae* biofilms) are associated with CRS phenotypes. Foreman and Wormald in a retrospective study showed for the first time that the presence of *S. aureus* biofilms is associated with a severe course of CRS, the surgical treatment of which does not provide reliable clinical improvement (Foreman & Wormald, 2010). Later, a prospective blind study confirmed these findings. Patients whose biofilm microbiome consisted of *S. aureus* had more severe objective symptoms, worse results of endoscopy of the nasal cavity after surgical treatment, and worse quality of life in general and required more postoperative examinations by a doctor compared to patients with other biofilm compositions. In the group of patients where single organism of *H. influenzae* biofilms was isolated, significantly less severity of disease was observed along with rapid recovery of nasal mucosa after surgical treatment (Singhal et al., 2011). These series of clinical observations and results have prompted the search for effective anti-biofilm therapy.

Biofilm-associated CRS treatment strategies. Strategies for combating biofilms have evolved to include the identification and application of anti-biofilm agents that target different stages of biofilm formation and maintenance. Key approaches include inhibiting biofilm formation through the disruption of quorum sensing pathways, preventing the initial attachment of microbial cells to surfaces, and disassembling mature biofilms by degrading the extracellular matrix or interfering with biofilm-specific signaling mechanisms. Additionally, novel antimicrobial compounds, including natural products such as herbal extracts and synthetic molecules, have been identified for their efficacy against biofilms. These compounds operate via diverse mechanisms, including the disruption of microbial communication, inhibition of cell adhesion, and degradation of the biofilm matrix, showcasing the multifaceted nature of biofilm-combating strategies (Roy et al., 2018).

In the context of otolaryngology, the search for new strategies to eliminate biofilms in patients with CRS is becoming more and more relevant as due to the increasing rate of antibiotic resistance, the spectrum of effective antimicrobial drugs that would effectively counteract the pathogenic flora in the microbiome of biofilms is gradually decreasing. Therapeutic pathways

aimed at eliminating biofilms in patients with CRS include

- antimicrobial neutralization;
- phage therapy;
- nanoparticles;
- dispersion of the structure of the formed biofilms;
- disruption of quorum-sensing system.

Antimicrobial neutralization. The extracellular matrix, which is a component of biofilms, protects the microorganisms inside from the immune defense mechanisms of the host organism and prevents the penetration of antimicrobial agents. In addition, in the biofilm, microorganisms develop resistance to antibiotics with the help of hereditary mechanisms of resistance, in particular, adaptive mutation and horizontal gene transfer (Manciula et al., 2020). Therefore, the effective elimination of biofilms with the help of traditional antibiotics is gradually becoming a difficult task.

It is logical that the decrease in the effectiveness of antibiotics due to the spread of antibiotic resistance prompted more detailed studies of existing antimicrobial agents, in particular macrolides. Antimicrobial drugs from a number of macrolides exhibit a bacteriostatic antimicrobial effect by inhibiting bacterial protein synthesis through reversible inhibition of the 50S bacterial ribosomal subunit. The use of macrolides has demonstrated that they potentially exert an anti-biofilm effect by inhibiting the production of key molecules involved in cellular quorum sensing (Walwork et al., 2006; Zhang et al., 2023). Although the exact mechanism of cell quorum antagonism remains unclear, it has been hypothesized that macrolides may indirectly affect an unidentified protein prior to the transcription of autoinducer synthase (Zhang et al., 2023).

Walwork et al. evaluated a cohort of 64 CRS patients in a prospective, double-blind, randomized, placebo-controlled study. Patients received roxithromycin therapy for 12 weeks or placebo, and outcomes were assessed using the Sino-Nasal Outcome Test-20 (SNOT-20) scale and the Likert scale . There was only a statistical decrease in SNOT-20 symptoms — by 0.4 points 12 weeks after the appointment of therapy and a decrease by 0.7 points according to the Likert scale, that is, no significant subjective improvement in the answers of patients obtained 12 weeks after the appointment of the therapy occurred, which calls into question the effectiveness of macrolide therapy over a long period (Walwork et al., 2006). This type of study delineates benefits related to the direct antimicrobial action of macrolides and efficacy specifically in the presence of biofilms and does not take into account the anti-inflammatory effect of macrolides in CRS (Wu et al., 2019; Lees et al., 2020).

The discrepancy between the described *in vitro* effects and the clinically valid benefit of the use of macrolides is highlighted in the meta-analysis by Pynnonen et al., which demonstrates that there is limited evidence to support the use of long-term macrolide therapy in CRS (Pynnonen et al., 2013). Although the meta-analysis demonstrated a statistical advantage of long-term macrolide therapy, changes by less than 1 point on the SNOT-20 scale are not clinically significant (Pynnonen et al., 2013). Further studies are needed to determine whether the *in vitro* anti-biofilm effect of macrolides can be used as monotherapy or in combination with other treatments to achieve sustained clinical improvement in patients with CRS.

Topical antibiotics have been the subject of research for a long time due to their ability to achieve significantly higher concentrations of the antibiotic dose on the mucosal surface of the paranasal sinuses with limited systemic absorption. In the study by Ha et al., artificial *in vitro* cultivation of biofilms of sensitive strains of *S. aureus* and their subsequent treatment with increased concentrations of local antimicrobial drugs are described. The study shows that topical application of mupirocin can reduce the microbial mass of *S. aureus* biofilm by more than

90%, while topical application of ciprofloxacin and vancomycin is virtually ineffective (Ha et al., 2008). A clinical study by Jervis-Bardy et al. demonstrated the short-term effectiveness of the sinus lavage with mupirocin solution for *S. aureus* infection in groups where outcomes after FESS were examined in 25 patients in whom surgery did not improve sinus clinical symptoms. A one-month randomized study was conducted, in which two groups of patients were created: in one group, an isotonic saline solution with the addition of 0.05% mupirocin was used for nasal irrigation twice a day, while in the control group, irrigation was performed with an ordinary isotonic saline solution twice a day and orally prescribed amoxicillin with clavulanic acid. After one month, culture results from the paranasal sinuses, in which no growth of pathogenic flora was found, were noted in 89% of patients in the mupirocin group, compared to 0% in the control group. In the mupirocin group, a statistically significant decrease in scores on the Lund-Kennedy scale was also found compared to the control group. It was found that effective exposure to culture results did not, however, lead to an improvement in subjective symptom scores relative to pretreatment baseline. In addition, re-evaluation of the mupirocin group 2-6 months after treatment showed that 83.3% of patients had positive cultures for *S. aureus* with the return of Lund-Kennedy scores to the initial level. Therefore, only short-term clinical effectiveness of local mupirocin therapy was observed (Jervis-Bardy et al., 2012). Moreover, the study shows that solutions for washing the nasal cavity containing mupirocin have a low level of antimicrobial effectiveness with long-term use: about 75% of applications are ineffective after 2—6 months from the beginning of therapy (Jervis-Bardy et al., 2012).

Attempts to develop a new antimicrobial agent are described. One such example is N,N-dichloro-2,2-dimethyltaurine (NVC-422), which is a synthetic and stable form of N,N-dichlorotaurine, a compound formed during the phagocytic antimicrobial oxidation reaction. NVC-422 has broad-spectrum antimicrobial activity with reliable efficacy against *S. aureus*, including methicillin-resistant strains, *Streptococcus pneumoniae*, *Escherichia coli*, and *Candida* spp., and viruses such as herpes simplex virus and adenovirus. Singhal et al. (2012) in their observations did not note the development of resistance to NVC-422 after serial target tests on the above-mentioned microorganisms. After the artificially induced development of *S. aureus* biofilms in the frontal sinus of a sheep, two irrigations into the cavity of the frontal sinus of a sheep with NVC-422 caused a dose-dependent decrease in biofilm biomass compared to those animals whose frontal sinuses were not treated with the drug: 0.11 ± 0. 11 $\mu m^3/\mu m^2$ after application of 0.5% NVC-422 solution compared to 2.01 ± 2.7 $\mu m^3/\mu m^2$ in the control group (Singhal et al., 2012). There have been no further publications regarding the effectiveness of the mentioned above agent. Considering its aggressive broad-spectrum antimicrobial activity, there is a relevant need of adequate probiotic support after future trials of NVC-422. This aspect of research calls to be widely revealed in the future.

Current literature describes the use of substances of natural origin as a means against biofilms in CRS (Roberts et al., 2022). One of these substances is manuka honey —monofloral honey from the manuka tree, a product of natural origin produced in New Zealand and Australia, the main active ingredient of which is methylglyoxal (MGO), has a high content of phenol, which has bactericidal properties. Application of manuka honey *in vitro* demonstrated significant bactericidal activity against planktonic and biofilm forms of *S. aureus* and *P. aeruginosa*, eliminating 82% of methicillin-susceptible *S. aureus*, 63% of methicillin-resistant *S. aureus* (MRSA) biofilms, and 91% of *P. aeruginosa* biofilms. Studies conducted on models of CRS in sheep revealed a statistically significant decrease in the microbial

mass of the biofilm compared to the application of washing with saline solutions at concentrations of 1.8 mg/mL MGO 0.676 ± 0.079 $\mu m^3/\mu m^2$ versus 0.114 ± 0.033 $\mu m^3/\mu m^2$, P = 0.001 and 3.6 mg/mL — 0.608 ± 0.101 $\mu m^3/\mu m^2$ versus 0.141 ± ± 0.039 $\mu m^3/\mu m^2$, P = 0.001. Animals treated with MGO alone showed more toxic effects, including severe sinus inflammation and respiratory epithelial metaplasia, compared to animals treated with MGO in manuka honey, suggesting the presence of natural anti-inflammatory properties of other honey components (Paramasivan et al., 2014; Roberts et al., 2022). Clinical trials investigating the reliable efficacy of manuka honey in CRS patients with biofilms have not been conducted to date.

After the use of antibiotics, there is a decrease in the diversity of the sinus microbiome with an increase in the share of non-commensal pathological species that form biofilms. Probiotics are increasingly recognized for their potential therapeutic role in sinonasal health, leveraging beneficial bacteria strains to counteract sinonasal inflammatory diseases and improve sinonasal microbiota composition.

To complement the microbiome, researchers examined *Lactobacillus* spp. that were found at high concentrations in mucosal samples from healthy humans and at low concentrations after antibiotic use in CRS patients (Liu et al., 2013; Jain et al., 2014). The presence of *Lactobacillus fermentum* in cultures with *S. aureus* and *P. aeruginosa* led to 40 — 50% destruction of pathological biofilms and marked inhibition of bacterial growth. After inoculation of mammalian cells *in vitro* with *S. aureus* and *P. aeruginosa*, the viability of mucosal cells decreased by 50—60%. In contrast, the presence of *L. fermentum* in addition to both pathogenic bacterial strains increased mucosal cell viability by 80—95%. Early *in vitro* studies are highly promising, with *Lactobacillus* spp. able to inhibit the growth, cytotoxicity, and biofilm-forming ability of several strains of *S. aureus* and *P. aeruginosa* (Ramakrishnan et al., 2015; Heredia-Castro et al., 2021). In a clinical setting, Mukerji et al. (2009) evaluated the use of probiotics as an adjunctive therapy in CRS. In this prospective placebo-controlled study, 77 patients were assigned to an oral probiotic *L. rhamnosus* group and an oral placebo group for 4 weeks. At the end of the study and patient interviews, no significant difference in SNOT-20 scores was observed (Mukerji et al., 2009).

A study performed by Cho et al. (2020) revealed results of the growth of 6 patient-derived and 1 laboratory strain of *P. aeruginosa* with and without *Lactococcus lactis*. *L. lactis* co-cultured with *P. aeruginosa* in the presence of mucin-induced growth in 1 strain, inhibited growth in another, and had no observable impact on the 5 other isolates. Mentioned effects were highly reproducible and consistent (Cho et al., 2020). Described in the same study, *L. lactis* introduced as a probiotic nasal rinse showed potential interactions with *P. aeruginosa*, a pathogen implicated in CRS, indicating its possible beneficial role in managing sinonasal microbiota and combating CRS.

Physical antimicrobial methods are also used to combat biofilms in CRS. Photodynamic therapy, as defined by the National Cancer Institute, is a method of treating precancerous diseases and malignant neoplasms, which is based on using a photosensitizer (a special drug) and lasers that generate radiation of a certain wavelength (Juarranz et al., 2008). Antimicrobial photodynamic therapy (aPDT) is a modern non-medicinal method that consists in the destruction of microorganisms by perforating cell membranes in the presence of photoreactive pigments. Activation of these compounds by exposure to laser light generates the synthesis of oxygen free radicals, which destroy the bacterial cell membrane, allowing the cell pigment to penetrate into structures where it can cause lethal cell damage. This therapy has shown promise in the elimination of planktonic bacteria and is able to significantly reduce the microbial mass of biofilm by more

than 99.9% *in vitro* (Biel et al., 2011). Also, research by Biel et al. (2013) investigated the effect of aPDT on biofilms in a polymer model of the human maxillary sinus cavity. Their experiments revealed a 5-fold reduction in the microbial mass of *P. aeruginosa* biofilms and a 3-fold reduction in the mass of MRSA biofilms after a single application (Biel et al., 2013). Previous studies by the same group showed that the use of aPDT does not cause damage to *in vitro* cultured human airway epithelial cells (Biel et al., 2012). The prospect of clinical application of aPDT is currently under investigation.

A promising area of research is the use of corticosteroids in CRS with biofilms in view of their effect on the immune system. It has been studied that corticosteroids enhance some functions of the native immune system of the nasal mucosa and paranasal sinuses, including increasing the production of complement and acute phase proteins. It was found that the use of high concentrations of fluticasone — 400 mg/200 mL, budesonide — 750—2000 mg/200 mL, and mometasone — 200—400 mg/200 mL directly reduces the microbial mass of the biofilm by 99% *in vitro* (Goggin et al., 2014). This fact prompts further research and clarification of new mechanisms of action of intranasal corticosteroids in the fight against bacterial biofilms.

Antimicrobial peptides (AMPs) therapy is emerging as a promising approach for combating biofilms in CRS patients, offering a novel strategy against biofilm-associated infections that are resistant to conventional antibiotics. The effectiveness of AMPs, such as the synthetic peptide D-LL-31, demonstrates significant potential in enhancing the biofilm-eradicating effects of currently used antibiotics like amoxicillin and tobramycin. For instance, Wongkaewkhiaw et al. highlighted the synergistic effect of D-LL-31 with these antibiotics, leading to a substantial decrease in the biofilm biomass and presenting a compelling case for its application in clinical settings (Wongkaewkhiaw et al., 2020). Furthermore, the study on DNase-mediated eDNA removal enhancing D-LL-31 activity against CRS biofilms opens a new avenue for combination therapies that target the structural components of biofilms, thus facilitating the penetration and efficacy of AMPs (Wongkaewkhiaw et al., 2020). These findings underscore the potential of AMPs not only as direct antimicrobial agents but also as enhancers of existing antibiotic treatments, offering a promising path forward in the management of CRS and CRS-associated biofilms. The exploration of AMPs in CRS treatment reflects a crucial step toward innovative solutions for biofilm-associated infections, marking a significant advancement in the fields of otolaryngology and infectious diseases.

Phage therapy. Bacteriophage (phage) therapy offers a promising alternative for combating biofilms in CRS patients addressing the limitations of traditional antibiotic treatments. Recent research has demonstrated that phages can effectively target and dismantle biofilms formed by *P. aeruginosa* and *S. aureus,* which exhibit resistance to antibiotics and contribute to the recalcitrance and exacerbation of the disease. For instance, Fong et al. (2017) observed that a phage cocktail significantly reduced biofilm biomass of *ex vivo P. aeruginosa* isolates from CRS patients, suggesting a potential novel treatment avenue (Fong et al., 2017). Similarly, Drilling et al. (2014) found that a phage cocktail was effective against *S. aureus* biofilms and planktonic forms in clinical isolates from CRS patients, highlighting the broad-spectrum capability of phage therapy (Drilling et al., 2014). The emerging evidence supports the potential of phage therapy not only in eradicating biofilms and multidrug-resistant bacteria but also as a safe and targeted treatment option for CRS, necessitating further clinical research to optimize phage formulations and treatment protocols for broader application in managing CRS and overcoming the challenges posed by bacterial biofilms.

Nanoparticles. Nanoparticle therapy represents a cutting-edge approach to combating biofilms in CRS patients, offering hope where traditional treatments falter. Nanoparticles, due to their small size and large specific surface area, can penetrate biofilms more effectively than conventional therapies, delivering antibacterial agents directly to the site of infection. For instance, ISMN-loaded poly-lactide-co-glycolide acid (PLGA) and polyethylene glycol (PEG) nanoparticles, conjugated with anti-*S.aureus* α-toxin, have demonstrated significant anti-*S. aureus* effects and the ability to effectively inhibit biofilm formation in a sheep CRS model without toxic effects, presenting a promising drug delivery system for CRS treatment (Huang et al., 2021). Additionally, the controlled release of silver nanoparticles (AgNPs) with silk-elastin-like protein-based polymers (SELPs) has shown potent antibacterial activity against *P. aeruginosa* and *S. aureus*, the most commonly virulent bacterial strains observed in post-operative CRS, highlighting the potential of nanoparticle-mediated therapies in preventing biofilm formation and enhancing post-surgical outcomes (Yathavan et al., 2023). These advancements not only offer a new arsenal against biofilms but also pave the way for more effective, targeted therapies for CRS. Further research into nanoparticle therapy holds the promise of revolutionizing the management of CRS, with the potential to reduce antibiotic resistance and improve patients' quality of life.

Dispersion of the structure of the formed biofilms. The search for novel therapeutic agents targeting biofilms in CRS reveals a growing interest in using compounds like mannosides, pilicides, curlicides, chelating agents, and polysaccharides due to their unique mechanisms of disrupting biofilm structure and function. While the specific studies directly addressing the efficacy of these agents in CRS are limited, the broader scientific inquiry into their application against biofilms offers promising insights.

Mannosides and pilicides, targeting the adhesion processes of bacteria, could potentially impair the initial steps of biofilm formation on sinonasal tissues. Curlicides, focusing on the disruption of curli fibers — an integral component of certain bacterial biofilms—offer another avenue for undermining biofilm integrity. Chelating agents, by sequestering metal ions crucial for biofilm stability and bacterial growth, could weaken the biofilm matrix, making it more susceptible to antimicrobial penetration and host immune responses. Polysaccharides, through their diverse biological activities, including immunomodulatory effects, could aid in altering the biofilm environment or directly attacking its structure. For instance, agents like xylitol have shown some efficacy *in vitro* against *S. epidermidis* biofilm biomass and planktonic bacteria of *S. aureus* and *P. aeruginosa*, suggesting a therapeutic potential in the management of CRS (Jain et al., 2016). Furthermore, the exploration of topical antibiofilm agents highlights the importance of identifying compounds with specific antibiofilm activity that may prove useful for treating biofilm-associated CRS (Hale et al., 2022). These innovative therapeutic strategies, targeting the biofilm's structural and functional integrity, represent a promising frontier in the treatment of CRS, potentially offering more effective management options for this complex and recalcitrant disease.

Another tactic to eliminate biofilms is the use of surface-active substances to disrupt the integrity of the biofilm. Chiu et al. (2008) investigated the use of baby shampoo as an anti-biofilm cleaner, as it is based on three different active ingredients which are chemical surfactants, namely PEG-80 sorbitan laurate, cocamidopropyl betaine, and sodium trideceth sulfate. 18 patients who underwent FESS were instructed to wash their sinuses with 1% baby shampoo in saline for 4 weeks after surgery. After 4 weeks, the authors observed an improvement in the SNOT-22 scale in 46.6% of the patients, and in 63% of the respondents, there was an improvement in

the sense of smell along with a significant decrease in the viscosity of mucous secretions and a decrease in postnasal congestion (Chiu et al., 2008). However, 10% of patients reported unbearable side effects — headache, burning in the nasal cavity, changes in the sense of smell. Despite the fact that washing with a shampoo solution inhibited the growth of biofilms, this therapy turned out to be completely ineffective in terms of their destruction (Chiu et al, 2008).

In a randomized, controlled trial performed by Farag et al. (2013), 44 patients with CRS participated were divided into two groups, one of which performed rinsing of the nasal cavity and paranasal sinuses with a solution with baby shampoo after FESS, and the other group performed rinsing with simple hypertonic saline solution. Both treatment groups showed similar improvements in symptoms and olfactory thresholds. However, 52% of the shampoo group had significant side effects, compared with only 5% of patients reporting side effects in the other group. In particular, washing with a solution with baby shampoo can cause a headache and a burning sensation in the nasal cavity, which, in general, significantly reduces the prospect of using it or any other cleaning agent as a therapy aimed at eliminating biofilms in CRS (Faraq et al., 2013; Tulaci et al., 2021).

Citric acid (zwitterionic surfactant; CAZS) is a relatively new type of surfactant consisting of citric acid, which chelates calcium in calcium ion bridges, which are an integral part of the biofilm structure and on which its integrity depends. CAZS makes it possible to separate the biofilm from the surface of the mucous membrane and subsequently dissolve it. Desrosiers et al. have demonstrated *in vitro* that CAZS is reliably effective in reducing colony-forming units of *S. aureus* and *P. aeruginosa*. It is associated with statistically significant reductions in *S. aureus* and *P. aeruginosa* biofilm microbial mass, which are similar to those achieved with hydrodynamic saline delivery, 2.5- and 2.9-fold reductions compared to 2, 3- and 2.4-fold decrease, respectively, $P < 0.002$. However, the most effective reduction in the microbial mass of biofilms was observed after hydrodynamic application of CAZS — a 3.9- and 5.2-fold reduction in the biomass of *S. aureus* and *P. aeruginosa*, respectively, $P = 0.001$ (Desrosiers et al., 2007). Some concern is caused by the further results of the *in vivo* study. Tamashiro et al. (2009) showed that CAZS is toxic to the ciliated epithelium: in an experiment on rabbits, CAZS caused neutralization of mucociliary clearance. The researchers observed 80—85% deciliation of the ciliated epithelium 1—3 days after treatment with 96.25% restoration of the ciliated epithelium 6 days after the cessation of CAZS therapy. The mucosa of the paranasal sinuses was more vulnerable to infection by microorganisms during the time period of the ciliated epithelium restoration (Tamashiro et al., 2009).

«SinuSurf», another surfactant-based cleanser specifically designed for nasal application, has demonstrated potent anti-biofilm effects *in vitro*, but was withdrawn from the market due to toxic effects (Kofonow et al., 2012). Today, despite the rather high efficiency in the fight against biofilms, the toxic effect of surface-active cleaning agents prevails over their therapeutic effectiveness (Rosen et al., 2013).

The use of targeting enzymes against the polysaccharides required for the formation of the matrix of biofilms is a potentially promising therapeutic strategy. Poly-N-acetylglucosamine (PNAG) is a polysaccharide that is produced by *S. aureus* and is critical for biofilm matrix formation. This polysaccharide is responsible for the acquisition by biofilm microorganisms of resistance to the immune peptides of the host, forming a powerful barrier that prevents the interaction of immune cells with bacterial proteins. Dispersin-B is an enzyme that cleaves PNAG and can be used for targeted destruction of the structure of biofilms (Eddenden et al., 2022). Breslawec et al. (2023) demonstrated both the prevention of *S. epidermidis* biofilm formation

and the detachment of previously formed biofilms *in vitro* after the use of Dispersin-B (Breslawec et al., 2023).

Extracellular DNA performs the function of stabilizing the biofilm matrix, transferring plasmids containing genes that form resistance and promote biofilm adhesion to surfaces. A bacterial deoxyribonuclease, NucB, produced by the marine bacterium *Bacillus licheniformis* has been investigated to potentially cleave extracellular DNA (Shields et al., 2013). In an inoculated biofilm from the culture obtained during FESS, NucB caused complete destruction of formed biofilms from nuclease-producing bacterial strains (*S. aureus, S. anginosus, S. lugdunensis, S. salivarius*) and induced a 33% reduction in biofilm formation, containing non-nucleate producer strains (*Corynebacterium* spp. and *Moraxella catarrhalis*). NucB was ineffective against bacteria in the planktonic form, acting exclusively on biofilm forms. The role of NucB in the destruction of biofilms in CRS remains poorly studied to date (Shields et al., 2013; Baslé et al., 2018).

Violation of cellular quorum sensing. Cell quorum sensing is an ability of some bacteria and other microorganisms to communicate and coordinate their behavior by secreting molecular signals.

One of the newest strategies to combat biofilms is the neutralization of quorum-sensing molecules synthesized by microorganisms. Lee et al. (2015) identified that the T2R38 gene, which is responsible for enhancing bitter taste perception, acts as a key stimulator of nitric oxide production, which subsequently leads to the activation of innate immunity against biofilms in CRS (Lee et al., 2015). T2R38 is activated in response to acetyl-homoserine lactone (AHL) molecules forming the cell quorum sensing system, synthesized by *P. aeruginosa* and other Gram-negative bacteria. Suppression of AHL molecules leads to the destructure of the biofilm of *P. aeruginosa*, which subsequently makes them more susceptible to surface-active substances and antimicrobial drugs. Genetic variations (mutations) of the T2R38 gene are associated with reduced ability to clear and eliminate bacteria in the upper respiratory tract and are also correlated with increased susceptibility to gram-negative sinonasal infections. Subsequent studies have indicated that T2R38 is a risk factor for CRS, which is further associated with the need for FESS (Lee et al., 2015). Adappa et al. (2014) compared T2R38 genotypes among 70 CRS patients who underwent primary FESS compared to a total of 347 CRS patients and found a significantly higher frequency of the non-functional genotype in the post-FESS patient cohort, X2 (2) = 6.526, P = 0.0383. Evaluation and determination of prospects for the use of agonists of the T2R38 gene as antibiofilm therapy are currently studied in more detail (Adappa et al., 2014).

As part of a study of *Pseudomonas* biofilms, it was shown that macrolide antibiotics reduce the expression of the las and rhl quorum sensing genes. Each system includes the transcription activator gene, lasR or rhlR, and the autoinducer synthase gene, lasl or rhll, which are required for the production of autoinducer molecules. In one of the studies, the expression of elastase and rhamnolipid, two extracellular virulence factors, the production of which is regulated by the cell quorum sensing systems las and rhl, respectively, was investigated under the influence of azithromycin. The expression of these virulence factors was negatively correlated with the levels of autoinducers in *Pseudomonas*. Azithromycin treatment caused an 80% decrease in lasI expression and a 50% decrease in rhlI expression, indicating a decrease in cellular quorum sensing activity. It is not known whether these rather promising results of *in vitro* studies give hope to assume a possible effect against biofilms in the complex biological environment in patients with CRS (Walwork et al., 2006). In the studies of Parween et al. (2023), it was shown that paraoxonases (PONs) play an important role in counteracting the formation of biofilms when they damage the

epithelium of the respiratory tract, in particular, in CRS (Parween et al., 2023). PONs are enzymes synthesized by the liver and kidneys; they are able to break down lactones, including AHL. *In vitro*, PON inactivates AHL and reduces the growth activity of *P. aeruginosa* biofilms (Aybey et al., 2016). In a new experimental model on Drosophila melanogaster, PON-transgenic insects showed increased survival after infection with *P. aeruginosa* and *Serratia marcescens* — both microorganisms use AHL to realize cell quorum sensing (Aybey et al., 2016). This understanding of innate immunity as a defense against biofilms is becoming increasingly important and raises the possibility of modulating the innate immune system for a better response against biofilms.

Conclusions. Chronic rhinosinusitis involves a complex interaction of various factors, both infectious and host organism factors. The predominant form of the existence of microorganisms in the biological environment is a biofilm. A number of new biofilm-targeting therapies for CRS are currently either in use or under development. However, the effectiveness of these methods and their potential integration into the armamentarium of strategies directed against CRS with biofilms are largely depend on a better understanding of the role of biofilm in the pathogenesis of chronic rhinosinusitis. Such understanding is the subject of several ongoing studies worldwide, as it points to the prospect of developing treatment strategies tailored to the specific causes of CRS in each individual patient.

Existing data convincingly confirm the role of biofilms in the pathogenesis and clinical course of CRS. Modern therapeutic strategies aimed at combating biofilms in CRS are at various stages of development. In general, they are aimed at i) neutralizing biofilm-forming microbes; ii) destruction of the structure of existing biofilms, and iii) violation of cellular quorum sensing.

In view of the perspective of otolaryngology, the most promising directions in combating biofilms are those that will be effective in conditions of antibiotic resistance — such are phage therapy, nanoparticle therapy, and the selection of antimatrix agents. Researchers will face a complex and long-term challenge that requires constant active research, considering the dynamically changing world of microorganisms and the constant modification of phenotypes of chronic rhinosinusitis.

The process of understanding biofilm function and its impact on the pathogenesis of CRS is a key to the development of new therapies that may expand and potentially change the CRS treatment paradigm. Based on this, there is undoubtedly huge potential for future research.

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БАКТЕРІАЛЬНІ БІОПЛІВКИ ПРИ ХРОНІЧНОМУ РИНОСИНУСИТІ.
КЛІНІЧНА РОЛЬ ТА СУЧАСНІ ТЕРАПЕВТИЧНІ СТРАТЕГІЇ

Біоплівки являють собою складну сукупність мікроорганізмів, які утворюються на біологічних та небіологічних поверхнях, формуючи міцну структуру завдяки міжклітинному матриксу. На відміну від планктонної форми існування, форма біоплівки дає змогу мікроорганізмам виживати в набагато більш несприятливих умовах та ефективніше розвивати резистентність до антимікробних препаратів. Згідно з сучасними літературними даними, з'являється все більше доказів того, що біоплівки мають вирішальне значення в патофізіології хронічних інфекцій в отоларингології, включаючи хронічний риносинусит. Ще донедавна розуміння ролі біоплівок було досить обмеженим. Останні досягнення в методах ідентифікації біоплівок і молекулярної біології висвітлили нове розуміння ролі біоплівок при хронічному риносинуситі. В сучасній отоларингології проблема бактеріальних біоплівок є однією з ключових з огляду на причини тяжкого перебігу хронічного риносинуситу. У статті проаналізовано нові дані стосовно клінічної ролі бактеріальних біоплівок при хронічному риносинуситі, а також висвітлено актуальні та перспективні терапевтичні стратегії протидії бактеріальним біоплівкам. Зокрема, приділено увагу альтернативним антимікробним засобам, таким як бактеріофаги, наноматеріали та антимікробні пептиди. Розкрито перспективу застосування антиматриксних та антиадгезивних методів. Також, як один із обнадійливих напрямків протидії біоплівкам, представлено методи впливу та порушення клітинного кворум-сенсингу.

Ключові слова: *бактеріальні біоплівки, хронічний риносинусит, елімінація біоплівок, антимікробні препарати, кворум-сенсинг.*