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THE ROLE OF BACTERIAL BIOFILM IN REFRACTORY CHRONIC RHINOSINUSITIS: A NARRATIVE REVIEW

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ABSTRACT

Objectives: Chronic Rhinosinusitis (CRS) is a common inflammatory disease impacting 5-12% of the population, leading to substantial morbidity and healthcare expenses. Bacterial biofilms on the sinonasal mucosa are a key factor in CRS's development, persistence, and resistance to treatment. This review explores their role in refractory CRS, focusing on structure, formation, impact on severity, and diagnostic/therapeutic approaches.
Methods: We conducted a comprehensive literature review using PubMed, Scopus, and Web of Science, searching for keywords related to CRS, bacterial biofilms, antibiotic resistance, and therapies. We prioritized studies from the last decade examining biofilms' impact on CRS pathogenesis, resistance, and novel treatments.
Key findings: Biofilms, organized microbial communities within an extracellular polymeric matrix, are significantly more resistant to antibiotics and host immune responses than free-floating bacteria. They form through stages: initial attachment, proliferation, and complex 3D structure development, with quorum sensing vital for maturation. Common CRS biofilm pathogens include Staphylococcus aureus, Pseudomonas aeruginosa, and Haemophilus influenzae. Biofilms correlate with more severe disease, poorer surgical outcomes, and higher recurrence. Diagnostics include electron microscopy, confocal laser scanning microscopy (CLSM), and molecular methods. Treatment involves surgical removal, topical antibiotics, and novel strategies like phage therapy, quorum sensing inhibitors, and micro-biome-based interventions.
Conclusions: Biofilms are critical in refractory CRS, causing persistence, treatment resistance, and worse outcomes. A deep understanding of biofilm mechanisms is crucial for effective diagnostics and therapies. Future research should standardize diagnostics, clarify biofilm-host interactions, and conduct trials on new, personalized biofilm-targeting treatments.

KEYWORDS

Bacterial Biofilm, Chronic Rhinosinusitis, Antibiotic Resistance, Endoscopic Sinus Surgery, Microbiome

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Introduction.

Chronic rhinosinusitis (CRS) is a common inflammatory condition affecting 5-12% of the general population and associated with significant morbidity and healthcare costs (Kariyawasam & Scadding, 2011). The presence of bacterial biofilms on the sinonasal mucosa has been established as a critical factor in the pathophysiology, persistence, and recalcitrance of CRS. CRS is characterized by inflammation of the paranasal sinus mucosa that persists for at least 12 weeks, with bacterial infections and biofilms contributing to its development and persistence (Koefoed et al., 2023; Vanderpool & Rumbaugh, 2023).

CRS is characterized by complex interactions between host-mediated factors, the external environment, and the sinus microbiota (Shaghayegh et al., 2022; Koefoed et al., 2023).

Patients commonly experience symptoms such as nasal blockage discomfort or pressure in the facial area, a diminished sense of smell, and copious thick nasal discharge. Standard first-line therapies, including sinus irrigation and topical corticosteroids, are commonly employed, yet a number of patients do not achieve satisfactory outcomes and may subsequently require functional endoscopic sinus surgery. The presence of biofilms on the sinonasal mucosa can exacerbate CRS, potentially leading to increased disease severity and treatment recalcitrance (Koefoed et al., 2023).

A key factor contributing to the persistence and recurrence of infections is biofilm formation, which significantly enhances antimicrobial resistance and ultimately results in therapeutic failures. These biofilms can induce inflammatory responses and may exhibit antibiotic resistance, complicating the condition and hindering treatment effectiveness (Vanderpool & Rumbaugh, 2023).

Background of Chronic Rhinosinusitis

The underlying mechanisms of CRS are heterogeneous and not entirely known, but alterations in mucociliary clearance, abnormalities in the sinonasal epithelial cell barrier, and tissue remodeling may contribute to the chronic inflammatory processes (Stevens et al., 2015). The role of bacterial biofilms in CRS is clinically significant due to their potential to cause resistance to both antimicrobial therapy and host defenses (Shaghayegh et al., 2022). Given the significant impact of biofilm infection on the quality of life of those afflicted with CRS, and the high costs to the healthcare system, an extensive understanding of how biofilms are implicated in CRS is vital (Huang et al., 2022). Affecting a large portion of the population across continents, chronic rhinosinusitis leads to significant healthcare costs.

The Significance of Biofilms in Chronic Infections

Multidrug-resistant bacteria, including methicillin-resistant Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus influenzae, exacerbate CRS by forming biofilms that resist antibiotic penetration (Shariati et al., 2021). Biofilms are structured communities of microorganisms encased in a self-produced extracellular polymeric matrix that enhances their resistance to environmental stresses, host immune responses, and antibiotic treatments (Shariati et al., 2021; Huang et al., 2022). These biofilms contribute to the persistence and severity of CRS, as well as the failure of antibiotic treatments (Vanderpool & Rumbaugh, 2023).

The persistent symptoms and bacterial presence despite antibiotic use may be attributed to the presence of biofilms in sinusitis patients, highlighting the importance of alternative strategies specifically designed to target and disrupt biofilm formation in order to improve treatment outcomes (Vanderpool & Rumbaugh, 2023).

Objectives of the Review

This review delves into the function of bacterial biofilms in refractory chronic rhinosinusitis, paying particular attention to potential therapeutic strategies capable of enhancing patient outcomes. Current research increasingly underscores the critical role of biofilms in the progression and persistence of chronic infections, highlighting the imperative for novel intervention methods. Such understanding is a key area of global investigation, as it directly informs the development of personalized treatment approaches tailored to the unique underlying causes of CRS in individual patients. Biofilm-associated infections are widespread globally, particularly in hospital settings, leading to higher rates of illness and mortality, increased healthcare expenditures, and extended hospital stays. Consequently, extensive research is warranted to explore new antibacterial agents and the intricate interactions between CRS and biofilms.

Methodology

This narrative review aims to integrate and present current scientific literature regarding bacterial biofilms in refractory chronic rhinosinusitis. It specifically examines their inherent structure, their operational function, and their broader clinical implications, with the goal of identifying promising therapeutic targets and developing effective strategies. Furthermore, the review underscores the critical importance of comprehending biofilm dynamics, as this understanding is essential for crafting precise treatments designed to disrupt biofilm formation and ultimately enhance therapeutic outcomes for patients.

Search Strategy

A comprehensive literature search was conducted using databases such as PubMed, Scopus, and Web of Science, with keywords including "chronic rhinosinusitis," "bacterial biofilms," "antibiotic resistance," and "therapeutic strategies" to identify relevant articles. The literature search primarily included studies from the last ten years, thereby ensuring the incorporation of the most recent findings.

Selection Criteria

Articles for this review were selected based on their contribution to understanding the impact of biofilms in refractory chronic rhinosinusitis, particularly concerning antibiotic resistance and innovative treatment strategies. The search exclusively included English-language publications that explored biofilm formation, resistance mechanisms, and potential therapeutic interventions, encompassing clinical trials, in vitro experiments, and comprehensive reviews.

Inclusion and Exclusion Criteria

Inclusion Criteria:

• Peer-reviewed articles published in English
• Studies focusing on bacterial biofilms in CRS
• Research examining diagnostic or therapeutic innovations
• Articles addressing public health implications
• Publications from 2014-2024 (with seminal earlier works included for historical context)
• Original research, systematic reviews, meta-analyses, and clinical trials

Exclusion Criteria:

• Non-English publications
• Conference abstracts without full-text availability
• Studies focusing solely on fungal biofilms
• Research limited to in vitro studies without clinical relevance
• Duplicate publications or overlapping study populations

Data Extraction

Relevant data were extracted and synthesized from the selected articles to provide a comprehensive overview of current knowledge and identify research gaps in the field. This synthesis offers deeper insight into the complexities of biofilm-related chronic rhinosinusitis and helps pinpoint potential directions for future research and clinical practice.

Results

Bacterial Biofilms: An Overview

Biofilms represent intricate microbial communities that adhere to surfaces and are encased in a self-produced matrix, offering a structural refuge that significantly enhances their resistance to antimicrobial agents and host immune defenses (Zabolotna & Maliarenko, 2024). This matrix, primarily composed of extracellular polymeric substances, creates a protective barrier that impedes drug penetration and shields bacteria from environmental stressors (Huang et al., 2022). Devising effective strategies against chronic infections critically depends on understanding the resistance mechanisms facilitated by biofilms. Such biofilms are particularly problematic in CRS due to their ability to withstand traditional antibiotic treatments, necessitating the exploration of alternative therapeutic approaches (Shariati et al., 2021; Huang et al., 2022).

In clinical practice, a major hurdle in effectively treating certain infections is the ability of bacterial biofilms to render standard, empirical antibiotic therapy ineffective. This means that when clinicians initiate treatment based on their best guess of the causative pathogen (empirical therapy), the presence of biofilms, which are protective communities of microorganisms, often leads to treatment failure because the antibiotics cannot adequately penetrate or eliminate the bacteria within these structured communities (Shariati et al., 2021). This necessitates a more targeted and often more complex approach to overcome the inherent resistance mechanisms conferred by biofilm formation. This has led to increased research toward new methods of biofilm detection, microbial diversity, and innovative treatment strategies (Maina et al., 2018). Biofilms' inherent resistance to antibiotics and the host's immune system may explain why CRS is so difficult to treat (Koefoed et al., 2023).

Formation and Structure of Biofilms

Biofilms typically develop in a series of stages, commencing with the adherence of planktonic bacterial cells to a surface, succeeded by proliferation and the creation of a complex three-dimensional structure (Moulic et al., 2024). The structural framework of bacterial biofilms is an intricate composite material, primarily consisting of an extracellular polymeric substance (EPS) matrix. This matrix is predominantly hydrated, with water constituting a significant proportion, and is further composed of a complex mixture of polysaccharides, nucleic acids (including extracellular DNA), and various proteins. These components interact synergistically to provide the biofilm with its characteristic mechanical stability, structural integrity, and protective properties against environmental stressors and antimicrobial agents.

Quorum sensing, a sophisticated cell-to-cell communication mechanism, is instrumental in orchestrating the formation and subsequent maturation of bacterial biofilms. This process is pivotal for bacterial adaptation and persistence within these complex microbial communities (Sahreen et al., 2022). Comprehending the stages of biofilm formation-from initial attachment to mature community development-is crucial for devising effective therapeutic interventions (Empitu et al., 2025; Shariati et al., 2021). Disrupting bacterial communication may be a promising method for developing anti-biofilm treatments (Brackman & Coenye, 2014).

Mechanisms of Biofilm Resistance

Biofilms employ a variety of mechanisms to resist antibiotics, including restricted penetration of antimicrobials, slow growth of biofilm-embedded cells, and the expression of specific resistance genes (Zabolotna & Maliarenko, 2024). Furthermore, bacteria within biofilms can exhibit up to a 1000-fold increase in resistance to antibiotics compared to their planktonic counterparts, highlighting the formidable challenge they pose in clinical settings (Lam et al., 2015; Huang et al., 2022). When antibiotics are administered, the bacteria deep within the biofilm may only be exposed to low concentrations, which can induce biofilm formation rather than suppress it (Huang et al., 2022). Understanding these resistance mechanisms is crucial for developing strategies to enhance antibiotic efficacy or explore alternative treatments (Vanderpool & Rumbaugh, 2023).

Common Bacterial Species in CRS Biofilms

Multidrug-resistant bacteria such as Pseudomonas aeruginosa, Staphylococcus aureus and Haemophilus influenzae are commonly found in CRS biofilms, which may contribute to the persistence and severity of CRS and antibiotic treatment failure (Huang et al., 2022). The interaction of multiple bacterial species within these biofilms further complicates treatment, creating synergistic relationships that enhance their collective resistance and inflammatory potential (Vanderpool & Rumbaugh, 2023). Several bacterial species, including Staphylococcus aureus, Pseudomonas aeruginosa, and Haemophilus influenzae, are commonly found in CRS biofilms, complicating treatment strategies (Foreman et al., 2009). These species are known for their ability to form robust biofilms, exacerbating inflammation and hindering mucosal healing (Zabolotna & Maliarenko, 2024).

Beyond the more commonly recognized pathogens, a range of opportunistic microorganisms can also be implicated in infections. These include coagulase-negative staphylococci, various Corynebacterium species, Streptococcus viridans, and Enterococcus faecalis. Furthermore, a number of anaerobic bacteria, such as Cutibacterium, Porphyromonas, Prevotella, Bacteroides, and Peptoniphilus, may contribute to the pathogenic burden (Kaliniak et al., 2024). The presence of these organisms often poses diagnostic and therapeutic challenges due to their varied clinical presentations and antimicrobial susceptibility profiles.

The Role of Biofilms in Chronic Rhinosinusitis

Biofilms are a key factor in the recalcitrant nature of CRS, contributing to the persistence of inflammation, resistance to antibiotic therapy, and the need for repeated surgical interventions (Zabolotna & Maliarenko, 2024). The presence of these biofilms fosters a protected environment, enabling persistent colonization and recurrent inflammation, which are hallmarks of CRS (Huang et al., 2022). CRS is characterized by inflammation rather than infection, but commensal microbes and pathogens contribute to the initiation and progression of mucosal inflammation (Mahdavinia et al., 2015). The ineffectiveness of antibiotics in treating sinusitis, despite positive culture results, may be attributed to biofilms, which exhibit distinct properties that contribute to their resilience and tolerance (Vanderpool & Rumbaugh, 2023).

Biofilms and the Pathogenesis of CRS

Specific bacterial species within sinonasal biofilms can significantly influence the characteristics and severity of CRS, further complicating pathogenic processes through polymicrobial interactions (Vanderpool & Rumbaugh, 2023). Understanding the complex interplay between bacterial virulence, host immune responses, and environmental factors is essential to elucidate the pathogenesis of CRS (Vanderpool & Rumbaugh, 2023). In addition, the close proximity of bacteria within biofilms facilitates horizontal gene transfer, promoting the spread of antibiotic resistance genes and adaptation to environmental stressors (Huang et al., 2022). This prompts the need to investigate the complex interplay between microbiome composition, host immunity, and inflammatory responses within the sinonasal cavity (Mahdavinia et al., 2015). Colonization and microbiota imbalance may initiate chronic immune responses and inflammation, while a dysfunctional immune barrier and obstructed sinuses can promote secondary bacterial overgrowth and dysbiosis, exacerbating CRS (Mahdavinia et al., 2015).

Impact on Inflammatory Response

The biofilms stimulate the host immune system, leading to chronic inflammation, tissue damage, and the perpetuation of CRS symptoms (Feazel et al., 2012). The biofilm structure itself is a three-dimensionally specialized community of microorganisms encased in an extracellular polymeric substance, which is capable of eliciting sustained immune responses (Długaszewska et al., 2015). This biofilm-associated inflammation leads to continuous recruitment of immune cells, such as neutrophils and eosinophils, further contributing to tissue remodeling and disease chronicity (Długaszewska et al., 2015). The secreted products of Staphylococcus aureus biofilms may also play a significant role in the inflammatory responses observed in CRS (Shaghayegh et al., 2022). Biofilm formation serves as a defense mechanism, protecting microbes from antibiotics and host immune responses, thereby potentially increasing enterotoxin production and further promoting inflammation (Mahdavinia et al., 2015).

Staphylococcus aureus biofilms, in particular, have been linked to T helper cell 2 pathway activation and eosinophilic inflammation, commonly observed in CRS with nasal polips patients (Koefoed et al., 2023). Some authors propose that biofilm development is related to Th1 inflammatory profiles, while Th2 inflammatory profiles are related to paranasal sinus inflammation (Długaszewska et al., 2015). This sets off a self-perpetuating cycle where biofilms stimulate the release of TGF-β1, which facilitates tissue remodeling and epithelial-to-mesenchymal transition, contributing to pathological structural changes and disease progression (Vanderpool & Rumbaugh, 2023). As mucus accumulates, it fosters pathogenic bacterial expansion and biofilm formation, contributing to a self-amplifying inflammatory feedback loop (Vanderpool & Rumbaugh, 2023).

Influence on Disease Severity and Recurrence

Biofilm presence is associated with more severe disease, poorer surgical outcomes, and a higher likelihood of recurrence (Hoggard et al., 2016; Shaghayegh et al., 2022). Patients with Staphylococcus aureus biofilms exhibit significantly higher preoperative disease severity and postoperative recurrence, while those with single-species Haemophilus influenzae biofilms may experience milder disease (Koefoed et al., 2023). Biofilms contribute to the recalcitrant nature of CRS by establishing a cycle of persistent infection, chronic inflammation, and tissue damage, which can lead to increased disease severity and frequent recurrence (Vanderpool & Rumbaugh, 2023). These biofilms can lead to longer postoperative reactive inflammatory signs of the nasal cavity and paranasal sinuses compared to patients without biofilms (Zabolotna & Maliarenko, 2024). Studies have also indicated that CRS patients with biofilms exhibit more severe symptoms, higher recurrence rates, and poorer outcomes following surgical interventions (Koefoed et al., 2023). Nonetheless, biofilms in CRS patients are associated with more severe symptoms, poorer outcomes, complicated postoperative courses, and an increased likelihood of revision surgery (Kaliniak et al., 2024).

Diagnosis of Biofilms in Chronic Rhinosinusitis

The detection and characterization of bacterial biofilms in chronic rhinosinusitis has evolved significantly over the past two decades. Following the initial identification of biofilms in CRS patients using scanning electron microscopy in 2004, advances in diagnostic methodology have provided crucial insights into their prevalence, composition, and clinical significance. This review analyzes current diagnostic approaches, their technical limitations, and emerging molecular techniques that may enhance future detection strategies.

Clinical Evaluation

The diagnosis of CRS is primarily based on clinical presentation, with symptoms persisting for 12 weeks or longer. Anterior rhinoscopy and nasal endoscopy are essential components of the physical examination, potentially revealing mucosal edema, purulent discharge, and anatomical abnormalities. However, these approaches cannot directly visualize or confirm the presence of biofilms, which requires more specialized techniques.

Radiological Assessment

Computed tomography (CT) and magnetic resonance imaging (MRI) are valuable for evaluating the extent of mucosal disease and anatomical abnormalities in CRS. However, these modalities cannot definitively identify bacterial biofilms. Some researchers have investigated the correlation between specific radiological features and the presence of biofilms, but findings remain inconsistent and non-specific.

The limitations of traditional diagnostic methods have driven the development and adoption of advanced imaging and molecular techniques specifically designed to detect and characterize biofilms in the sinonasal cavity.

Advanced Imaging Techniques

The visualization and characterization of bacterial biofilms in chronic rhinosinusitis require sophisticated imaging modalities that can identify the distinctive three-dimensional architecture and composition of these microbial communities. Several advanced microscopy techniques have emerged as valuable tools for biofilm detection in research and, increasingly, in clinical settings.

Traditional Diagnostic Methods

The detection and characterization of bacterial biofilms in chronic rhinosinusitis has evolved significantly over time, with methodologies ranging from basic culture techniques to sophisticated molecular approaches. Traditional diagnostic methods remain important in clinical practice but present various limitations in the context of biofilm detection

Scanning Electron Microscopy

Scanning electron microscopy (SEM) represents one of the earliest and most widely employed methods for direct visualization of biofilms on sinonasal mucosa. Scanning electron microscopy (SEM) has been widely utilized to visualize biofilm architecture on sinonasal mucosal specimens (Długaszewska et al., 2015). SEM utilizes electron beams to generate high-resolution surface topography images of mucosal specimens. The morphological criteria for biofilm identification typically include the presence of spherical or elliptical structures (smaller than 5 μm) surrounded by extracellular polymeric matrix, sometimes with visible water channels (Koefoed et al., 2023; Shaghayegh et al., 2022). Studies employing SEM report biofilm prevalence in CRS patients ranging from 25% to 80%, with healthy controls demonstrating either no biofilms or significantly lower prevalence (Koefoed et al., 2023)

Despite its historical importance, SEM demonstrates considerable limitations. The technique cannot reliably distinguish bacteria from similarly sized non-bacterial structures or differentiate bacterial extracellular matrix from host-derived mucus, resulting in low specificity (Shariati et al., 2021). Moreover, the morphological criteria employed for biofilm identification lack biofilm-specific molecular markers, introducing subjectivity into the diagnostic process. SEM also fails to identify bacterial species within biofilms, limiting its utility in guiding targeted antimicrobial therapy (Huang et al., 2022; Koefoed et al., 2023).

Transmission Electron Microscopy

Transmission electron microscopy (TEM) has been utilized, often complementing SEM, to examine the internal ultrastructure of biofilms by generating high-resolution two-dimensional images (Koefoed et al., 2023). While TEM provides detailed visualization of biofilm architecture, it shares many of SEM's limitations, including inadequate specificity, lack of species identification capability, and reliance on morphological criteria that lack molecular specificity (Shariati et al., 2021). Additionally, sample preparation for both SEM and TEM may introduce artifacts that complicate interpretation.

Confocal Laser Scanning Microscopy

Confocal laser scanning microscopy (CLSM) has emerged as the second most commonly employed technique for biofilm detection in CRS. For microscopic visualization, Confocal Laser Scanning Microscopy (CLSM) employs two primary fluorescent labeling strategies: the BacLight LIVE/DEAD kit, which serves as a universal probe for assessing cell viability, and fluorescence in situ hybridization (FISH), a species-specific probe for targeted microbial identification. These fluorescent markers, when excited by laser exposure, allow for three-dimensional reconstruction of biofilm topography (Shariati et al., 2021; Vanderpool & Rumbaugh, 2023).

CLSM demonstrates several advantages over electron microscopy, including improved specificity with the ability to distinguish bacteria from host structures. When employing FISH, CLSM can identify specific bacterial species within biofilms, potentially facilitating the study of polymicrobial interactions in CRS pathogenesis. Estimates of biofilm prevalence using CLSM range from 44% to 90% in CRS patients, with healthy controls rarely demonstrating biofilm presence (Shariati et al., 2021). Combining BacLight and FISH techniques significantly enhances the ability to identify biofilm-positive Chronic Rhinosinusitis (CRS) patients, outperforming either method used in isolation (Koefoed et al., 2023).

Despite these advantages, CLSM remains limited by the vague criteria defining biofilm presence. Typically, intense fluorescence of a particular size surrounded by less intense fluorescence (representing the matrix) constitutes biofilm formation, introducing subjectivity into interpretation. FISH techniques are further constrained by the need for prior knowledge of bacterial species to select appropriate probes, limiting broad-spectrum screening capabilities (Shariati et al., 2021). Additionally, CLSM requires specialized equipment and expertise not routinely available in clinical settings.

In Vitro Culture and Biofilm Formation Assays

Microtiter plate assays represent a distinct approach to biofilm detection, focusing on the in vitro biofilm-forming capacity of bacteria isolated from CRS patients rather than direct detection in mucosal samples. Studies employing this methodology have reported that 28.6% to 84% of swabs from CRS patients contain bacteria with biofilm-forming capabilities (Shariati et al., 2021; Vanderpool & Rumbaugh, 2023).

While this technique offers advantages of relative sensitivity, cost-effectiveness, and clinical feasibility, it provides an indirect assessment of biofilm presence. The capacity of bacteria to form biofilms under in vitro conditions does not reliably predict their ability to form biofilms in vivo. Additionally, standard culture-based techniques often fail to comprehensively characterize the entire sinus microbiota, primarily due to the considerable diversity of bacterial species present and the inherently slow growth rates of bacteria within biofilm structures (Koefoed et al., 2023; Vanderpool & Rumbaugh, 2023).

Histological Examination

Histological staining techniques, including hematoxylin and eosin (H&E) and Toluene Blue, have been employed to visualize biofilm masses in mucus and bacterial aggregates within the extracellular polymeric substance (EPS) matrix. These methods can simultaneously assess tissue response and biofilm presence, offering the advantage of integration with routine histopathological processing. However, they require invasive tissue sampling and may lack specificity without additional confirmatory techniques (Vanderpool & Rumbaugh, 2023).

Emerging Molecular Approaches

The limitations of conventional microscopy and in vitro techniques highlight the need for more robust molecular methods for biofilm detection. Two promising approaches include biofilm gene-targeted polymerase chain reaction (PCR) and RNAscopeTM.

Biofilm gene-targeted PCR involves the detection and amplification of genes or transcripts associated with biofilm formation, introducing a quantitative dimension absent in microscopic techniques. When combined with conventional culture methods, PCR could provide more reliable evidence of biofilm formation without relying on the subjective judgment of microscopists. Ideally, RNA transcripts represent the optimal target as they reflect active expression of biofilm genes rather than merely their genomic presence. However, RNA's inherent instability presents significant technical challenges (Koefoed et al., 2023).

RNAscopeTM, a novel histological technique utilizing probes specific to particular RNA sequences, holds considerable promise for future biofilm detection. This methodology allows signal amplification (fluorescence or enzyme-mediated chromogens) while maintaining spatial distribution information. By combining bacterial probes (both species-specific and universal) with biofilm gene-specific probes, RNAscopeTM could enable in situ visualization of complete biofilm morphology relative to sinonasal architecture. Additionally, it offers the potential to distinguish between biofilm-associated and planktonic bacteria within clinical samples (Shariati et al., 2021).

Despite their promise, these molecular approaches face significant limitations. No universal biofilm gene has been identified, restricting analysis to species-specific biofilm-related genes (e.g., ica from Staphylococcus aureus, psl/alg/pel from Pseudomonas aeruginosa, and pdgX/luxS/dps/hktE from Haemophilus influenzae). Current protocols remain costly, labor-intensive, and require specialized expertise not routinely available in clinical settings (Shariati et al., 2021; Koefoed et al., 2023).

Clinical Applications and Limitations

Despite the array of available diagnostic methodologies, detection of bacterial biofilms in CRS faces substantial clinical challenges. Current gold-standard techniques (SEM, TEM, CLSM) require invasive tissue sampling, specialized equipment, and technical expertise that limit routine clinical implementation. The lack of standardized, objective criteria for biofilm identification further complicates diagnostic reliability and reproducibility. Additionally, recent studies have identified bacterial biofilms on the sinonasal mucosa of healthy individuals, suggesting they may represent a normal component of the respiratory mucosal environment. This observation complicates the interpretation of biofilm presence in disease pathogenesis, potentially reflecting a secondary consequence of chronic mucosal immune dysfunction rather than a primary pathogenic factor (Shaghayegh et al., 2022).

The diagnosis of bacterial biofilms in CRS has significantly advanced through various microscopic, culture-based, and emerging molecular techniques. While SEM, TEM, and CLSM have provided valuable research insights,

their clinical application remains limited by technical demands, cost, and interpretative challenges. In vitro assays offer accessible alternatives but provide only indirect evidence of biofilm involvement.

Future diagnostic approaches will likely transition from current labor-intensive electron microscopy or in vitro culture methods toward molecular techniques with improved accuracy, sensitivity, and clinical feasibility. The development of a rapid, quantitative, and non-invasive method for biofilm detection represents a critical unmet need in CRS management. Advances in molecular diagnostics targeting biofilm-specific genes or transcripts hold promise for enhancing diagnostic precision and guiding personalized therapeutic strategies. Until such techniques are validated for clinical use, the diagnosis of biofilm-associated CRS will continue to rely on a combination of clinical suspicion, therapy response patterns, and specialized laboratory investigations primarily confined to research settings.

Treatment Strategies

The management of biofilm-associated CRS represents a significant therapeutic challenge due to the inherent resistance of biofilm communities to conventional antimicrobial approaches. Current treatment strategies employ multiple modalities aimed at biofilm disruption, bacterial eradication, and restoration of sinonasal mucosal function. Good strategy needs multidisciplinary approach, including clinical microbiology, surgery, internal medicine, pharmacology, and basic science, to combat biofilm infections effectively (Wu et al., 2014; Zhang et al., 2020).

Treating bacterial biofilms in Chronic Rhinosinusitis patients increasingly emphasizes finding alternative therapeutic options beyond systemic antibiotics (Shariati et al., 2021). This shift in approach comes from the growing understanding that traditional methods often fail against established biofilms, requiring new strategies that specifically target the weaknesses of these biofilm structures.

Antibiotic Therapy

Systemic antibiotics often fall short in treating infections linked to biofilms because these bacterial communities are notoriously tough to tackle. Diseases caused by biofilms tend to come and go, are hard to reliably grow in lab cultures, and display significant antibiotic resistance (Foreman et al., 2009). This resilience largely comes from the bacteria within the biofilm having slower metabolism, the antibiotic struggling to penetrate the protective extracellular polymeric matrix, and the bacteria boosting their defenses like efflux pumps. Topical antibiotic delivery represents an important advancement, allowing achievement of higher local drug concentrations while minimizing systemic exposure. Topical treatments are a straightforward way to get around these issues because they deliver a consistent, high concentration of antibiotics directly to the sinonasal mucosa, allowing the medication to penetrate the biofilm with very little getting absorbed into the rest of the body (Shariati et al., 2021).

New ways to deliver antibiotics are constantly being developed, such as antibiotic-eluting sinus stents that release medication locally over time. For example, in one study, a ciprofloxacin-azithromycin sinus stent (CASS) significantly reduced biofilm mass in an experimental setting (Shariati et al., 2021). Such approaches may overcome the limitations of conventional delivery methods by maintaining therapeutic concentrations at the biofilm interface over extended periods.

Combination antibiotic therapies targeting different bacterial physiological states within biofilms show promise for enhanced efficacy. Certain antibiotic combinations demonstrate synergistic activity against biofilm communities through complementary mechanisms of action (Huang et al., 2022). However, the optimal antibiotic combinations, concentrations, and treatment durations remain to be defined through rigorous clinical trials.

Surgical Interventions

For biofilm-associated Chronic Rhinosinusitis that doesn't respond to medication, surgical management remains a primary treatment. Endoscopic sinus surgery (ESS) is crucial as it allows for the removal of affected tissue, restores proper sinus airflow and drainage, and enhances the effectiveness of topical medications; its core objectives in CRS are to clear obstructions, establish lasting drainage, and, when necessary, remove significant inflammation (like polyps, trapped mucus, or new bone growth) to open the sinuses for future topical therapy (Hildenbrand et al., 2024).

Extended ESS approaches may offer advantages for severe, biofilm-associated CRS.

For severe cases of Chronic Rhinosinusitis (CRS), extended endoscopic sinus surgery (ESS) offers improved results and a reduced need for follow-up surgeries compared to more limited functional procedures,

all without increasing surgical risks (Hildenbrand et al., 2024). This more extensive approach may facilitate more complete removal of biofilm-containing mucosa and improved access for postoperative topical therapies.

The presence of biofilms has been consistently linked to less favorable surgical outcomes; specifically, the formation of biofilms by Staphylococcus aureus and Pseudomonas aeruginosa is associated with a poorer post-operative course in patients undergoing surgery for chronic sinusitis and nasal polyposis (Foreman et al., 2009). This highlights the importance of aggressive postoperative management to prevent biofilm recurrence.

In pediatric CRS, adenoidectomy represents an important surgical intervention given the role of adenoid tissue as a potential biofilm reservoir. Adenoidectomy is considered the initial surgical choice for this condition, demonstrating success rates ranging from 50% to 71% when performed as a standalone procedure (Hildenbrand et al., 2024). When adenoidectomy fails, ESS may be indicated with reported success rates of 71-100%.

Postoperative care following sinus surgery increasingly incorporates strategies targeting biofilm prevention and eradication. Mechanical debridement through saline irrigations helps remove debris and disrupts early biofilm formation. Additionally, postoperative antibiotic irrigations may reduce bacterial burden and biofilm development during the healing phase (Mahdavinia et al., 2015).

Novel Approaches

The limitations of conventional therapies have spurred development of innovative approaches specifically targeting biofilm physiology and the host-pathogen interface in CRS. These emerging strategies offer potential advantages through biofilm-specific mechanisms of action.

Bacteriophage therapy is emerging as a promising alternative for treating infections linked to biofilms. For instance, a specific mixture of Staphylococcus aureus-targeting phages, known as CT-SA, was able to break down 94% of bacterial samples and notably shrink the overall biofilm mass in a study (Shariati et al., 2021). The high specificity and self-amplifying nature of phages offer theoretical advantages over conventional antimicrobials, though clinical translation requires further investigation.

Approaches using nitric oxide (NO) are gaining traction because this gas has both antimicrobial properties and the ability to break apart biofilms. Higher concentrations of NO have been shown to reduce Staphylococcus aureus biofilm mass isolated from CRS patients, with new delivery methods like liposomal encapsulation and polymeric carriers looking promising in lab studies (Shariati et al., 2021).

Quorum sensing inhibition represents a sophisticated approach targeting bacterial communication systems essential for biofilm formation and virulence.

Treatments that target quorum sensing work by disrupting bacterial communication systems, such as the accessory gene regulator (agr) locus, which is crucial for Staphylococcus aureus virulence (Kaliniak et al. 2024). Compounds like staquorsin, which specifically inhibit the agr system, show potential as new therapeutic agents.

Microbiota-based approaches are changing how we treat infections by focusing on restoring a healthy microbial balance rather than just eliminating pathogens. For instance, when healthy donors' nasal washes were used for nasal microbiota transplantation (NMT), patients saw significant, long-lasting relief from symptoms, accompanied by a stable increase in both the diversity and number of beneficial bacteria (Kaliniak et al., 2024; Shekhar et al., 2025). This method highlights how crucial a balanced microbiome is in preventing harmful bacteria from taking over and forming biofilms.

Antimicrobial peptides (AMPs) present a promising new direction, but there's a tricky balance between their ability to fight microbes and their potential harm to the host. For example, LL-37 (also known as human cathelicidin hCAP18) can combat Staphylococcus aureus and Pseudomonas aeruginosa biofilms, yet using high concentrations of these peptides can unfortunately trigger inflammation and damage to cilia (Shariati et al., 2021).

Public Health and Healthcare System Impact

Economic evaluations consistently demonstrate the substantial financial impact of biofilm-associated CRS on healthcare systems. Direct costs include increased physician visits, diagnostic procedures, medication expenses, and surgical interventions. Indirect costs encompass productivity losses, disability payments, and reduced quality of life measures.

Research reveals significant disparities in access to advanced diagnostic technologies and innovative treatments. Rural populations, underserved communities, and patients with limited insurance coverage face barriers to optimal biofilm-associated CRS management, contributing to persistent health inequities.

Studies examining healthcare technology adoption show variable implementation of advanced diagnostic methods across different healthcare settings. Academic medical centers demonstrate higher utilization rates of sophisticated diagnostic technologies compared to community healthcare facilities.

Discussion

Implications for Healthcare Delivery

The identification of bacterial biofilms as a critical factor in refractory CRS has profound implications for healthcare delivery models and clinical practice patterns. Traditional approaches emphasizing systemic antibiotic therapy and conventional surgical techniques prove inadequate for addressing the complex pathophysiology of biofilm-associated disease. This necessitates fundamental shifts in diagnostic protocols, treatment strategies, and patient management approaches.

The integration of advanced diagnostic technologies into routine clinical practice faces multiple barriers. Cost-effectiveness analyses reveal that while sophisticated diagnostic methods provide superior accuracy, their implementation requires substantial initial investments in equipment, training, and infrastructure development. Healthcare systems must balance the potential for improved patient outcomes against resource allocation constraints and competing priorities.

The recognition of biofilm involvement in CRS requires enhanced clinical decision-making frameworks that incorporate technological assessment capabilities. Clinicians must develop competencies in interpreting advanced diagnostic results while maintaining focus on patient-centered care approaches. This evolution demands comprehensive professional development programs and interdisciplinary collaboration models.

Societal and Public Health Implications

The prevalence of CRS and its association with biofilm formation necessitates comprehensive population health strategies addressing prevention, early detection, and equitable treatment access. Public health initiatives must consider environmental factors, social determinants of health, and community-specific risk factors that contribute to biofilm development and persistence.

Disparities in access to advanced diagnostic and therapeutic technologies create concerning health equity challenges. Rural and underserved populations may lack access to specialized otolaryngology services, advanced imaging capabilities, and innovative treatment options. Addressing these disparities requires targeted policy interventions, telemedicine integration, and resource allocation strategies that prioritize equitable healthcare access.

The emergence of biofilm-associated CRS as a significant public health challenge demands policy responses addressing technology adoption, reimbursement mechanisms, and quality improvement initiatives. Healthcare policies must evolve to support innovation adoption while ensuring appropriate utilization and cost-effectiveness.

Limitations of Current Treatments

Even with major progress in understanding how biofilms cause disease in Chronic Rhinosinusitis, consistently effective treatments remain a significant challenge (Fastenberg et al., 2016). Current treatment approaches face multiple limitations that must be addressed to improve clinical efficacy.

The heterogeneous and polymicrobial nature of sinonasal biofilms complicates therapeutic targeting. Staphylococcus aureus is often found in polymicrobial biofilm formations, suggesting that the full scope of diseases involving multiple bacterial species might be underestimated due to current testing limitations (Foreman et al., 2009). This diversity necessitates broad-spectrum or multi-targeted approaches rather than single-pathogen strategies. Antibiotic penetration into biofilm structures remains suboptimal even with topical delivery.

The extracellular polymeric substance (EPS) matrix in biofilms significantly hinders the penetration of many antimicrobial agents, and the metabolically inactive persister cells within these biofilms are naturally tolerant to antibiotics designed for active bacteria (Huang et al., 2022). These combined factors are key contributors to the pronounced antibiotic resistance commonly seen in biofilm-related infections (Foreman et al., 2009).

The persistent and recurring nature of biofilm-associated Chronic Rhinosinusitis (CRS) highlights our struggle to fully eliminate these bacterial communities. The existence of biofilms is linked to more severe sinus issues and less successful treatment results. This ongoing cycle of inflammation unfortunately sets the stage for biofilms to re-form even after initial treatment success.

Even with their vital role in treatment, standard surgical methods might not fully resolve biofilm problems. The presence of biofilms has been linked to poorer post-surgical outcomes for chronic sinusitis and

nasal polyps (Foreman et al., 2009). This underscores the critical need for surgical strategies specifically designed to tackle biofilms around the time of an operation to get better results.

The absence of a standardized way to detect biofilms makes both research and clinical decisions harder (Silva et al., 2021). The fact that biofilms are found at similar rates in both Chronic Rhinosinusitis patients and healthy individuals raises questions about their exact role in CRS, highlighting the urgent need for better methods to tell the difference between harmful and harmless biofilms (Hoggard et al., 2016).

Potentials for Personalized Medicine

The complexity and heterogeneity of biofilm-associated CRS necessitate individualized therapeutic approaches based on patient-specific factors. Emerging evidence supports stratification of patients according to microbiome profiles, inflammatory endotypes, and biofilm characteristics to guide personalized interventions.

Microbiome-guided therapies are a promising new area in personalized medicine. Since the sinus microbiota differs among chronic rhinosinusitis types and can even predict surgical success, analyzing a patient's microbiome could help in choosing the best treatment. This might involve nasal microbiota transplantation (NMT) - using nasal washes from healthy donors-potentially combined with local zinc, for patients with specific bacterial imbalances (Kaliniak et al., 2024).

Analyzing biofilm composition can help direct targeted therapeutic approaches. Molecular diagnostics could offer a more comprehensive understanding of the bacterial communities present and even provide a "molecular antibiogram" to guide treatment choices. This would make it easier to select the best antimicrobial treatments based on the specific pathogens in each patient. Furthermore, host factors, such as inflammatory endotypes, are increasingly shaping personalized management strategies. The fact that patients with chronic rhinosinusitis have sinus microbiota that differ in both composition and function, leading to varying immunological and clinical outcomes, points to a significant opportunity for therapies tailored to specific endotypes.

Biomarker-based treatment selection offers another promising path for personalized medicine. Several potential biomarkers, such as zinc status, MMP levels, and endotype analysis, could help guide the choice of individualized therapies (Kaliniak et al., 2024). Such approaches may allow more precise matching of therapeutic modalities to patient-specific disease mechanisms.

Areas for Future Research

Substantial knowledge gaps remain regarding biofilm pathophysiology and optimal management in CRS. Future research priorities should address these limitations to advance our understanding and improve clinical outcomes.

Standardized diagnostic approaches for clinically relevant biofilms are urgently needed. Comparative microbiome studies will offer crucial insights for selecting appropriate antimicrobial therapies and evaluating their effectiveness (Boase et al., 2013). Development of reliable, accessible biofilm detection methods suitable for clinical application would facilitate both research and patient care.

Mechanisms of biofilm-host interactions require further elucidation.

It is critical to fully understand the relationship between biofilms and both mucosal inflammation and immune responses, as this knowledge could uncover new targets for therapeutic intervention. Investigation of the bidirectional relationship between biofilms and host immunity may provide insights into disease pathogenesis and treatment resistance.

Clinical trials evaluating new strategies against biofilms are urgently needed. Ideally, these trials should be double-blind and placebo-controlled to thoroughly investigate and determine the best ways to administer, dose, and schedule these novel therapies for effectively inhibiting and treating biofilm-associated Chronic Rhinosinusitis (Shariati et al., 2021). Such trials should incorporate standardized outcome measures to facilitate comparison across studies.

The role of the sinonasal microbiome in biofilm formation and persistence requires further investigation. Chronic rhinosinusitis with nasal polyps is marked by an imbalance in the nasal microbiota, which suggests that adjusting this microbial community could be a promising therapeutic approach (Chalermwatanachai et al., 2018). Understanding the ecological relationships within the sinonasal microbiome may inform novel approaches to restore healthy microbial communities.

We need to systematically evaluate the long-term effectiveness of current and new treatments. Longitudinal molecular studies-which track changes over time-that assess how antibiotics, endoscopic sinus surgery, and topical treatments affect the types and amounts of microbes in Chronic Rhinosinusitis patients

would be extremely valuable (Ramakrishnan et al., 2015). These studies would offer vital insights into how long treatments last and what causes the condition to return.

Conclusions

Biofilms represent a critical factor in the pathophysiology of refractory chronic rhinosinusitis, contributing to disease persistence, treatment resistance, and poorer clinical outcomes. The complex, three-dimensional bacterial communities encased within extracellular polymeric substances demonstrate remarkable resistance to host immune responses and conventional antimicrobial therapies. This review has highlighted several key findings regarding biofilms in CRS:

First, biofilm detection requires sophisticated imaging and molecular techniques, with confocal scanning laser microscopy coupled with fluorescence in situ hybridization emerging as the current gold standard. However, standardized approaches for clinical biofilm detection remain an unmet need in the field.

Second, in vitro biofilm models provide valuable insights into biofilm formation and therapeutic susceptibility but cannot fully recapitulate the complex host-microbe interactions occurring in the sinonasal environment. More physiologically relevant models incorporating host factors are needed to bridge this translational gap.

Third, standard treatments like antibiotics and surgery aren't very effective against existing biofilms. Diseases driven by biofilms often come and go, are hard to reliably grow in cultures, and show extreme resistance to antibiotics (Foreman et al., 2009). This resistance necessitates novel approaches specifically targeting biofilm physiology.

Fourth, emerging strategies including topical antimicrobial delivery, natural products with antibiofilm properties, bacteriophage therapy, and microbiota-based approaches show promise for improved management of biofilm-associated CRS.

However, robust clinical trials are essential to confirm their effectiveness and safety before they can be widely used in patient care.

Finally, the diverse makeup of biofilms and varied host responses point toward the potential for personalized therapeutic approaches. These could be tailored based on individual microbiome profiles, inflammatory endotypes, and specific biofilm characteristics. Notably, the sinus microbiota differs among chronic rhinosinusitis phenotypes and can even predict how well surgery will succeed.

Clinical Implications

The recognition of biofilms as a key factor in refractory CRS carries significant implications for clinical management. Clinicians should maintain a high index of suspicion for biofilm involvement in patients with recalcitrant disease despite appropriate medical therapy, particularly those with evidence of specific pathogens like Staphylococcus aureus or Pseudomonas aeruginosa. Management of biofilm-associated CRS requires a multifaceted approach incorporating mechanical debridement through surgery, topical antimicrobial delivery, and strategies to prevent biofilm reformation. In severe instances, extended Endoscopic Sinus Surgery might be necessary. This approach allows for a more thorough removal of biofilm-laden mucosa and ensures better delivery of topical therapies after surgery (Hildenbrand et al., 2024). Current evidence supports aggressive postoperative care with saline irrigations and potentially topical antimicrobials to prevent biofilm recurrence following surgical intervention. The importance of patient education and adherence to maintenance therapy cannot be overstated in this context. Emerging therapeutic approaches including natural products, bacteriophages, and microbiota-based strategies may offer additional options for patients with refractory disease, though their clinical application awaits validation through rigorous trials. As these novel modalities transition from bench to bedside, they may significantly expand our therapeutic armamentarium. Finally, a personalized medicine approach incorporating microbiome analysis, inflammatory endotyping, and potentially biofilm characterization may optimize treatment selection for individual patients. As our understanding of the complex interactions between biofilms, host factors, and the sinonasal microbiome continues to evolve, so too will our ability to tailor therapeutic strategies to patient-specific disease mechanisms.

The management of biofilm-associated CRS represents a significant challenge requiring collaboration between otorhinolaryngologists, microbiologists, immunologists, and other specialists. Through continued research and clinical innovation, we may ultimately overcome the formidable barrier that biofilms present in the treatment of this common and morbid condition.

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