Biofilms in CRS

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REVIEW ARTICLE

Biofilms in chronic rhinosinusitis: 
Pathophysiology and therapeutic strategies

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Biofilm

aggregates of microorganisms in which cells are embedded in a self-produced matrix of extracellular polymeric substances (EPS) that are adherent to each other and/or a surface.
life cycle

Fig. 1 The biofilm life cycle.\textsuperscript{10}
biofilm detection methods:
Scanning electron microscopy (SEM)
Transmission electron microscopy (TEM)
Fluorescence in situ hybridization (FISH)
Confocal laser scanning microscopy (CLSM).
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<th>Table 1</th>
<th>Diagnostic criteria for biofilm-associated infections.</th>
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<td>Pathogenic bacteria must be associated with a surface</td>
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<td>Direct examination of infected tissue must demonstrate aggregated cell clusters encased in a matrix, which may be of bacterial or host origin</td>
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<td>Infection must be confined to a particular site of a host</td>
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<td>Recalcitrance to antibiotic treatment despite demonstrated susceptibility of planktonic bacteria on sensitivity testing</td>
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<td>Culture-negative results in the setting of a clinically documented high suspicion for infection</td>
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<td>Evidence of ineffective host clearance as demonstrated by the presence of biofilm colonies in discrete areas in host tissue associated with host inflammatory cells</td>
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Bacteria exist in two distinct forms: biofilm and planktonic. Biofilm is the preferred state in which an estimated 99% of bacteria exist. The bacteria that constitute a biofilm display several critical differences in regard to growth dynamics and genetic expression relative to their planktonic counterparts.
Once attached, bacteria begin to proliferate and secrete an extracellular matrix composed of polysaccharides, nucleic acids, and proteins. This matrix protects the biofilm against harmful factors in the environment.
Quorum sensing

It refers to the ability of bacterial cells to communicate. It is a cell density-dependent signal transduction process that allows for rapid coordination of behavior to stimulating factors in environment.

Biofilms can adapt to fluctuating levels of nutrients, competitive microorganisms, and toxic materials.

Antimicrobial resistance

Biofilms harbor a $10 - 1000$ fold higher resistance to antimicrobials than planktonic bacteria.

This resistance is due to:
- Extracellular matrix
- Bacterial stress response
- Quorum sensing
Mature biofilms are structured in a stacked, multilayered topography; cells in the deeper layers are subject to a different environment than those in the more superficial layers.

Interior regions of the biofilm are typically starved of nutrients and oxygen, suppressing metabolism and growth rate as part of the bacterial stress response.
Is the cell in dormant state within the deep interior of a biofilm likely contribute to the recalcitrant nature of biofilm-mediated infections. Persister cells are able to endure high concentrations of antibiotics and promote infection by relocating to other host sites and forming new biofilms harboring the same resistant phenotype as the original population.
Foreman et al
Culture of CRS biofilm:
Staph. aureus 50%
Pseudo. aeruginosa 22%
H. influenza 28%

Fungal biofilm

Foreman et al 2009

fungal biofilms in 11/50 (22%) of CRS patients with 7 of these cases demonstrating concomitant infection with Staph

SEM studies:
mucosa of CRS patients with biofilm-positive disease is markedly damaged compared to biofilm-negative mucosa. The severity of damage ranges from morphologic changes such as disarrayed cilia to reduced ciliary beat frequency to the complete absence of cilia.

There is increasing evidence that the presence of biofilms alters chemokine production, which may potentiate CRS. The production of interleukin-5, interleukin-6, and eosinophilic cationic protein is increased in the setting of biofilms.

biofilms were associated with poor clinical improvement following surgical intervention. Prince et al showed that patients with recalcitrant CRS after FESS were more likely to harbor biofilm-forming bacteria.

CRS patients with bacterial biofilms had worse preoperative imaging scores and, at a median of 8 months follow-up, these patients were more likely to have ongoing post-operative symptoms relative to patients without biofilms.

Pt with S. aureus biofilms:
Worse objective symptom scores.
Worse nasal endoscopy scores.
Worse quality of life outcomes.
Required more post-operative visits.

Treatment strategies

1) Antimicrobial neutralization
2) Dispersion of existing biofilms
3) Disruption of quorum sensing
Macrolides have been shown to, potentially, harbor an anti-biofilm effect through their inhibition of the production of key molecules.

Wallwork et al
Patients received either 12 weeks of roxithromycin therapy or placebo.

There was a statistically significant decrease in SNOT-20 by 0.4 points 12 weeks after therapy, and a 0.7-point drop in the patient response scale. No statistically significant decreases in patient response were noted after 12 wks.

Critically, this type of study does delineate between benefits related to the direct antimicrobial action of macrolides versus the anti-biofilm effect, and does not account for the anti-inflammatory effect of macrolides in CRS.
Topical antibiotics

Ability to deliver significantly higher doses of antibiotic to the sinonasal mucosal surface with limited systemic absorption.
Ha et al
S. aureus susceptible to were allowed to form biofilms in vitro then subjected to topical antimicrobials: Mupirocin reduce the biofilm mass by more than 90% ciprofloxacin and vancomycin were both largely ineffective

Jervis-Bardy et al

Efficacy of mupirocin sinonasal rinses against S. aureus infection in surgically recalcitrant CRS in RCT of 25 patients after FESS:

Patients were randomized
1 month of BID nasal saline rinses with 0.05% mupirocin
1 month of BID daily nasal saline rinses with oral Augmentin.

Results:
negative cultures were noted in 89% of patients in the mupirocin group compared to 0% in the placebo group.

Mupirocin group patients have a statistically significant reduction in LundeKennedy endoscopic scores relative to the control arms.
Interestingly, this microbiologic benefit did not translate into symptom score improvements relative to the pre-treatment baseline.
re-assessment of the mupirocin treated cohort at 2-6 months posttreatment demonstrated that 83.3% of participants developed positive cultures for S. aureus with a return of LundeKennedy scores to baseline.

Subsequent studies demonstrate that mupirocin rinses have a microbiologic failure rate of 75% over time.
Nonantibiotic antimicrobial

N,N-dichlorotaurine (NVC-422) generated during the phagocytic antimicrobial oxidative burst efficacy MRSA, S. pneumoniae, Escherichia coli, Candida species, and viruses such as herpes simplex and adenovirus

After establishment of S. aureus biofilms in the frontal sinuses of sheep, two sinus irrigations with NVC-422 induced a dose dependent reduction in biomass relative to untreated sinuses

No further study

Methylglyoxal (MGO) bactericidal.
Eliminates:
- 82% of MSSA
- 63% of MRSA biofilms
- 91% of P. aeruginosa biofilms

Animals given MGO alone were noted to have more toxic effects, including severe sinus inflammation and metaplasia of respiratory epithelium, compared to animals treated with MGO in the presence of Manuka honey suggesting natural anti-inflammatory properties in other components of the honey.

A recent study found that high concentrations of:
fluticasone   (400 mg/200 mL)
budesonide    (750 -2000 mg 200 mL)
mometasone    (200e400 mg/200 mL)
directly reduced biofilm biomass by up to 99% in vitro.

Chiu et al. use of baby shampoo as an anti-biofilm
18 pts, post FESS were instructed to irrigate their
sinonasal cavities with 1% baby shampoo in saline
for 4 weeks post-operatively.

At 4 weeks: 46.6% improvement in pt SNOT-22
scores and a 63% improvement in olfaction with a
significant decrease in mucus thickness and post-
nasal

10% of patients reported intolerable side effects. Furthermore, although shampoo rinses inhibited biofilm growth, this therapy failed to eradicate biofilm.

Citric acid/Zwitterionic surfactant (CAZS) is a novel surfactant consisting of citric acid, which chelates calcium in the calcium ion bridges integral to biofilm structural integrity. The zwitterionic surfactant is then able to detach the biofilm from the mucosal surface and force it into solution.
Desrosiers et al
CAZS induced statistically significant reductions in S. aureus and P. aeruginosa biofilm biomass

Tamashiro et al
CAZS to be toxic to cilia in a rabbit model
deciliation of 80% - 85% 1-3 days after treatment with
96.25% recovery 6 days after stopping CAZS, leaving
the sinuses more susceptible to infection in that time frame

Thank u