EMERGING DIRECTIONS IN THE TREATMENT OF CRSWNP & AERD/SAMTER’S TRIAD

A Glimpse Into the Future

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DISCLOSURES

None relevant to this Presentation
OBJECTIVES

• Chronic rhinosinusitis & AERD: definitions, epidemiology, and impact

• Making a Case for New Treatment Platforms

• Immunologic & Inflammatory Factors in CRS

• Novel immunomodulating therapies - Evidence

• Summary
CHRONIC RHINOSINUSITIS (CRS): DEFINITION

• An inflammatory condition involving the mucosa of the nose and paranasal sinuses for 12 weeks or longer

• Diagnosis now requires objective evidence of mucosal inflammation

• 1/3 of CRS pts have NP burden
CHRONIC RHINOSINUSITIS: EPIDEMIOLOGY

• Affects 10-15% of US population (Lund 2008)

• Burden on health system & economy
  • 27 million outpatient and ED visits annually
  • 5th most common diagnosis for which antibiotic prescribed
  • Lower QOL scores than COPD, CHF, back pain, angina
  • Treatment costs
  • Reduced productivity, absenteeism, disability
  • $6 billion and 50-73 million days of reduced productivity annually
PRESSING NEED FOR EFFECTIVE ADJUVANT THERAPIES FOR CRSWNP…

- Oral steroids have ~ 2 week maximal effect, that is short lived
- One annual steroid depot injection = risk for diabetes and osteoporosis
- Severe CRS receiving several steroid bursts per year: 43% osteoporosis, 49% secondary adrenal insufficiency

Repeated oral steroid (and antibiotic) use cannot be a long-term solution for CRS

IMMUNOLOGIC FACTORS IN CHRONIC RHINOSINUSITIS

Diagram:
- Innate
- Adaptive
- Host
- Fungi
- Bacteria
- Biofilms
- Superantigen
Superantigen should have some connection to the immune side to show the relatedness of bacteria and immunity

Peter, 10/26/2013
INNATE IMMUNITY IN CRS

- Initial line of antimicrobial defense
- Impaired Mucociliary clearance impaired in CRS
- Loss of Toll-like receptors in CRS
  - Pattern recognition of conserved microbial motifs
  - Reduced natural antimicrobial molecules/peptides in CRS
SKEWED ADAPTIVE IMMUNITY AND CRS

- Abundant evidence implicates **adaptive immune dysfunction** in CRS
- *S. aureus* biofilms in CRS noted to induce **Th2 skewing** of immune response
  - Response required biofilm +/- superantigen
  - *H influenzae* biofilms did not induce Th2 skewing
  - Suggests complex interaction between certain biofilms and host
- Resultant elevation of **IL-4, IL-5, IL-13, eosinophilic cationic protein**
- Influx of eosinophils
IMMUNOMODULATION STRATEGIES

• Target key cytokines

• Target key immunoglobulins
IMMUNE SYSTEM: THERAPEUTIC TARGETS

• CRS with nasal polyposis
  • Biofilm +/- superantigen response
    • $T_H^2$ driven high levels of IL-4, IL-5 and IgE within polyps

• IL-5 regulates chemotaxis, activation, and survival of eosinophils

• Local eosinophilic inflammation causing tissue damage
ANTHI-IL-5 (MEPOLIZUMAB)

• Mepolizumab: humanized anti-IL-5 antibody

• Randomized, controlled phase II trial (Gevaert 2011)

• 30 subjects with CRSwNP refractory to steroids
  • Treatment arm: 20
  • Placebo arm: 10

• 2 IV administrations 28 days apart

P. Gevaert et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. JACI. 2011 128(5):989-95.e1-8.
MEPOLIZUMAB: OUTCOMES

• At 2 months:
  • 12 of 20 patients had significantly reduced polyps
  • Only 1 of 10 placebo patients was improved
  • No statistically significant change in symptom measures

P. Gevaert et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. JACI. 2011 128(5):989-95.e1-8.
WHY WAS ANTI-IL-5 THERAPY EFFECTIVE IN ONLY HALF OF PATIENTS?

• Earlier study suggested IL-5 level in nasal secretions predicted response to drug (Gevaert 2006)

• No change in nasal IL-5 seen in phase II study (Gevaert 2011)

• Presumably reflects no change in nasal eosinophilia (not directly measured)

• Traditionally, eosinophil seen as key mediator of cell damage and polyp formation

• Recent evidence suggests that mast cells may have a critical role to play

P. Gevaert et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. JACI. 2011 128(5):989-95.e1-8.
TARGETING MAST CELLS/OMALIZUMAB

• Mast cell degranulation dependent on IgE

• **OMALIZUMAB** (anti-IgE monoclonal antibody)
  • For uncontrolled moderate-to-severe asthma
  • 3 mechanisms:
    • Binds circulating IgE suppressing serum levels
    • Competitively inhibits IgE receptor
    • Downregulates IgE receptors on mast cells, basophils, dendritic cells

P. Gevaert et al. Omalizumab is effective in allergic and nonallergic patients with NPs and asthma. JACI 2013 Jan;131(1):110-6.e1
OMALIZUMAB (XOLAIR): STUDY DESIGN

- RCT (Gevaert 2013)
  - 24 allergic and non-allergic subjects with polyps and asthma
  - Treatment arm: 16
  - Placebo arm: 8

- SQ injections
  - Q2 weeks (x8 injections)
  - Q4 weeks (x4 injections)

- Primary outcome: Lund-Mackay CT scores
- Secondary outcomes: Various QOL factors

P. Gevaert et al. Omalizumab is effective in allergic and nonallergic patients with NPs and asthma. JACI 2013 Jan;131(1):110-6.e1
ANTI-IL-4/IL-13 THERAPY (DUPILUMAB)

- Human anti-IL-4 **RECEPTOR** Ab
  - Blocks both IL-4 and IL-13 binding

- Past benefit seen in pts with other TH2 mediated dz
  - Asthma
  - Atropic dermatitis
  - CRSwNP??


**MFNS = Mometasone**

**Dupilumab subQ:**
- 600 mg loading dose
- 300mg weekly x 16

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**DUPILUMAB TRIAL FOR CRSWNP**

86 Patients assessed for eligibility

- **26 Excluded**
  - 10 Nasal polyp score <5
  - 5 Technical or administrative reason
  - 2 SinoNasal Outcome Test score <7
  - 2 Receipt of prohibited therapy
  - 2 Potential nonadherence to study procedures
  - 2 Had hepatitis B or C
  - 1 Had liver injury
  - 1 Informed consent not signed
  - 1 Underwent prohibited nasal surgery
  - 1 Met asthma exclusion criteria

60 Randomized

- 30 Randomized to receive placebo plus MFNS
  - 30 Received treatment as randomized

- 30 Randomized to receive dupilumab plus MFNS
  - 30 Received treatment as randomized
Decline in TH2 Biomarkers with SubQ Dupilumab

**Total serum IgE**

**Serum Eotaxin**
THE FUTURE FOR BIOLOGICS??

• Expensive
  • Is treatment more effective and less expensive than repeat surgery? Long term adjuvant treatment?
  • Insurance Coverage (in US)??

• Toxicity profile
  • Concerns for malignancy, cardiovascular disease, anaphylaxis
  • Nasopharyngitis + injection site reactions – 50%
AERD IS A SEVERE SUBTYPE OF CRSWNP & GOES BY MANY NAMES

Samter’s Triad

Nasal Polyps

Asthma

Aspirin Intolerance

Samter’s Triad
AERD PATIENTS SHOW DELAYED PRESENTATION IN THE 3\textsuperscript{RD} OR 4\textsuperscript{TH} DECADE

- Rhinitis
- Nasal Polyposis
- Asthma
- Aspirin Intolerance

AERD PATIENTS DO NOT TOLERATE STRONG COX-1 INHIBITORS

- Aspirin most common
  - 41% Ibuprofen
  - 4% Naproxen
  - 1% Ketorolac

ASPIRIN INTOLERANCE IS A “PSEUDOALLERGIC” REACTION

- Aspirin exposure is a marker of disease
- Reaction is 30-120 minutes after aspirin ingestion
- Typical Reaction involves Upper and Lower Airways
  - Possible conjunctivitis, rash, anaphylactoid reaction
  - NOT a Type I IgE Hypersensitivity
  - “Metabolic Disorder/Metabolic Allergy”
FESS FOR AERD

- Reduce Inflammatory burden and improve delivery of topical medicinals
- Ideally performed just prior to ASA desensitization
  - FESS OK on low-dose aspirin (81 mg)
- Improves asthma outcomes

- Need for revision surgery as much as 10x greater
- Greater CT disease severity compared to aspirin tolerant patients

ADJUVANT THERAPIES FOR AERD/SEVERE CRSWNP DISEASE

• ASA Desensitization
  • Effect on CRS>Asthma
  • Full effect may take up to 3 months, usually noticeable within days to weeks

• Zileuton
  • 5-LO inhibitor

• Montelukast?
  • Leukotriene Receptor Antagonist

• Omalizumab
  • Anti-IgE
1 SLIDE ON PATHOPHYSIOLOGY

- AERD is an acquired disorder of arachidonic acid metabolism

- **Decreased** prostaglandin E2 production

- **Increased** metabolism via 5-LO pathway

- The hallmark is marked overproduction of Cysteinyl Leukotrienes
  - Via 5-Lipoxygenase pathway (5-LO)

- Platelet adhesion theory for ASA effects
AERD IS CONFIRMED BY POSITIVE ASPIRIN CHALLENGE

- Oral, Bronchial, or Nasal Provocation
  - Similar sensitivity and specificity
  - Titrated to upper/lower airway reaction, measured by FEV1 or nasal peak flow

<table>
<thead>
<tr>
<th>Time</th>
<th>Day 0 (or 1)</th>
<th>Day 1 (or 2)</th>
<th>Day 2 (or 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>Placebo</td>
<td>20-40 mg†</td>
<td>100-160 mg</td>
</tr>
<tr>
<td>11 AM</td>
<td>Placebo</td>
<td>40-60 mg</td>
<td>160-325 mg</td>
</tr>
<tr>
<td>2 PM</td>
<td>Placebo</td>
<td>60-100 mg</td>
<td>325 mg†</td>
</tr>
</tbody>
</table>

Stevenson DD. Curr Allergy Asthma Rep 2009;9:155-63
EVIDENCE FOR EFFICACY WITH ASA DESENSITIZATION

- 173 consecutive desensitized AERD patients followed by telephone survey
- Compared to year before desensitization, report decreased asthma hospitalizations, sinus surgeries, ASA use
  - 14% discontinued in 1st year due to ASA side effects
  - 11% discontinued by another physician
  - 14/16 treatment failures had severe atopy

Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease

M. Pilar Berges-Gimeno, MD, a Ronald A. Simon, MD, b and Donald D. Stevenson, MD b La Jolla, Calif

EVIDENCE FOR LONG TERM EFFICACY WITH ASA DESENSITIZATION IN AERD

Limitation:

1) Retrospective

2) No control population as likely below standard to deny ASA following FESS

~ 3 YEAR CONTROL OF POLYP RECURRENT FOLLOWING FESS

Table 2. Changes in Endoscopic Polyp Grade during Aspirin Desensitization following Endoscopic Sinus Surgery (n = 21).a

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Right</th>
<th>Left</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>2.8 ± 1.2</td>
<td>3.1 ± 1.1</td>
<td>5.6 ± 1.2</td>
</tr>
<tr>
<td>POD 7</td>
<td>0.2 ± 0.4b</td>
<td>0.1 ± 0.3b</td>
<td>0.3 ± 0.5b</td>
</tr>
<tr>
<td>POD 28/AD day 0</td>
<td>0.4 ± 0.5c</td>
<td>0.2 ± 0.4d</td>
<td>0.6 ± 0.8d</td>
</tr>
<tr>
<td>Post-AD 1 month</td>
<td>0.3 ± 0.5</td>
<td>0.3 ± 0.5</td>
<td>0.5 ± 0.9</td>
</tr>
<tr>
<td>Post-AD 6 months</td>
<td>0.2 ± 0.4</td>
<td>0.1 ± 0.3</td>
<td>0.3 ± 0.7</td>
</tr>
<tr>
<td>Post-AD 12 months</td>
<td>0.4 ± 0.5</td>
<td>0.3 ± 0.5</td>
<td>0.6 ± 0.7</td>
</tr>
<tr>
<td>Post-AD 18 months</td>
<td>0.5 ± 0.6</td>
<td>0.3 ± 0.5</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td>Post-AD 24 months</td>
<td>0.5 ± 0.3</td>
<td>0.3 ± 0.4</td>
<td>0.7 ± 0.5</td>
</tr>
<tr>
<td>Post-AD 30 monthsa</td>
<td>0.4 ± 0.3</td>
<td>0.3 ± 0.4</td>
<td>0.6 ± 0.4</td>
</tr>
</tbody>
</table>

Abbreviations: AD, aspirin desensitization; POD, postoperative day; SD, standard deviation.

aData are expressed as mean ± SD.
bP < .001.
cP = .002.
dP = .001.
aData are based on a subcohort of 13 patients.

**FINAL ASA DOSAGES DURING ASA DESENSITIZATION**

| Table 3. Success Rate of Aspirin Desensitization following Endoscopic Sinus Surgery According to Final Maintenance Dose of Aspirin. |
|---|---|---|---|
| **Dose** | **325 mg qd** | **325 mg bid** | **650 mg bid** |
| **Response** | **Success, No.** | 4 | 8 | 8 |
| | **Failure, No.** | 0 | 1 | 0 |
| | **Success rate, %** | 100.0 | 88.9 | 100.0 |

Abbreviations: bid, twice a day; qd, once a day.

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PROMISING FUTURE FOR IMMUNOMODULATION ADJUVANT THERAPY IN CRSWNP DISEASE

- New strategies are needed to:
  - Forego surgery in some cases
  - Maintain post-FESS results
  - Limit NP recurrence/health costs of revision FESS
  - Limit prednisone and antibiotic use

- Durable “cure” will likely be dependent on modification of underlying immuno-inflammatory microenvironment

- Biologic agents and medicinals (ASA) can target these components of the immuno-inflammatory system
• Compelling evidence for clinical efficacy of biologics in NP dz is here
  • **Mepolizumab (anti-IL5)**
  • **Omalizumab (anti-IgE)**
  • **Dupilumab (anti-IL4-receptor)**
  • Phase III trials using biologics are underway

• AERD represents a unique subtype of difficult to treat CRSwNP dz with need for disease-specific medical therapies

• **ASA densensitization** represents an important adjuvant therapy for sinus surgeons
MICROBIAL AND IMMUNE FACTORS IN CHRONIC RHINOSINUSITIS
CHRONIC RHINOSINUSITIS: MICROBIAL FACTORS

- Nadel (1998):
  - 507 endoscopically guided cultures (265 patients)

- Often polymicrobial

- Fungus
  - 91.3% of CRS patients have positive fungal cultures
  - 91.3% of control patients have positive fungal cultures (Braun 2003)
  - Fungus contributed to AFRS
  - Unlikely to be central to CRS

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative rods</td>
<td>34.3%</td>
</tr>
<tr>
<td>Staph aureus</td>
<td>31.3%</td>
</tr>
<tr>
<td>Coagulase negative Staph aureus</td>
<td>44.2%</td>
</tr>
</tbody>
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BACTERIAL BIOFILMS AND SUPERANTIGEN
BIOFILMS

• Biofilm characteristics
  • Adherent to mucosa
  • Embedded in self-produced ECM
  • Quorum sensing allows coordination
    • Recruitment of new bacteria
    • Production of matrix
    • Biofilm maturation
    • Intraspecies and Interspecies communication

• Biofilm is preferred state of existence
  • <1% of bacteria exist in planktonic form

• >75% of microbial infection attributable to biofilm
BIOFILM LIFECYCLE

I. Planktonic Bacterial Cells

II. Attachment

Flagella

sad genes

Programmed mobilization
or physical detachment
by shearing

III. Monolayer

Proliferation

Type IV pili and twitching motility
sad genes

IV. Microcolony

Quorum sensing
last-dependent
signaling

V. Mature Biofilm

Head and Neck Surgery
BACTERIAL SUPERANTIGENS

- *S. aureus* secretes high-molecular-weight proteins: Enterotoxins

- Superantigens bypass APCs and directly activate T-cells

- Uncontrolled polyclonal activation of up to 25% of T cell population

- Cascade of proinflammatory cytokines

- Downstream activation of effectors: eosinophils, macrophages, mast cells
SUPERANTIGEN AND BIOFILMS

• Biofilm protects superantigen-producing *S aureus* from antimicrobials and immune surveillance

• Phenotypic conversion from planktonic to biofilm form associated with increased toxin secretion

• *Accessory gene regulator (agr)* locus modulates quorum sensing
  • Critical in biofilm formation AND toxin production

• Therapies that destroy biofilm may suppress superantigen
BIOFILMS IN CHRONIC RHINOSINUSITIS

• Prince (2008): 157 consecutive CRS patients
  • 30% with bacteria exhibiting biofilm-forming capacity
  • 70% of biofilms are Pseudomonas or S. aureus

• Biofilms detected in 30-100% of CRS patients

• Commonly polymicrobial
  • S. aureus interacts with hyphae of Candida in vitro
  • Modification of S. aureus virulence factor expression
  • Fungal biofilms may facilitate clinical infection by S. aureus

• Biofilms contribute to the chronic inflammation of CRS
BIOFILM EFFECTS ON PATIENT OUTCOMES

- Prospective, blinded study of 51 CRS patients undergoing FESS (Psaltis 2010)

- Bacterial biofilms in 71%

- Pre-op, biofilm patients had:
  - Worse radiology scores ($p = 0.003$)
  - Worse nasendoscopy scores ($p = 0.01$)

- Post-op (median follow-up 16 mo)
  - Worse sinus symptoms ($p = 0.002$)
  - Worse nasendoscopy scores ($p = 0.026$)
THERAPEUTIC IMPLICATIONS OF BIOFILMS

- Biofilms show 1000-fold less sensitivity to antibiotics
- Physical barrier to antibiotic penetration
- Activation of bacterial general stress response
- Differentiation to resistance phenotype
  - Downregulation of transmembrane channels
  - Upregulation of resistance genes
  - Increased expression of efflux pumps
- Dissemination of resistance genes by quorum sensing
BIOLUMINESCENCE STRATEGIES

• Antimicrobial / Superantigen neutralization

• Mechanical Disruption

• Quorum-sensing interruption
BIOFILM-TOXIC ANTIMICROBIALS
SYSTEMIC ANTIBIOTICS

• Typical doses do not achieve adequate anti-biofilm or anti-superantigen concentration
  - *S. aureus* biofilms from CRS patients grown in vitro (Desrosiers 2007)
  - MIC level of moxifloxacin had no effect on biofilm
  - MIC x1000 was required for a log 2 (>99%) reduction
  - Despite high dose treatment, viable bacteria remain
  - Similar results with *P. aeruginosa* biofilm and tobramycin
TOPICAL MUPIROCIN

- *S. aureus* most commonly cultured pathogen in recalcitrant CRS after FESS

- Mupirocin
  - Effective *in vitro* against *S. aureus* biofilms
  - Reduction of biomass >90%
  - Directly suppresses superantigen production by *S. aureus*
TOPICAL MUPIROCIN: CLINICAL EFFICACY

- Double-blind RCT (Jervis-Bardy 2012)
  - 25 *S. aureus* positive CRS patients randomized:
    - 1 month of 0.05% mupirocin nasal rinses BID
    - 1 month of saline rinses BID with Augmentin
TOPICAL MUPIROCIN: CLINICAL EFFICACY

- QOL scores:
  - Variable effect across studies
    - 75% reported improved QOL following nasal mupirocin x3 weeks (Uren 2008)
    - More recently, no change in QOL seen relative to baseline (Jervis-Bardy 2012)
  - Eradication of *S. aureus* does not consistently correlate with symptom improvement

- Transient *anti*-S. *aureus* effect achieved with mupirocin but not sustained
  - Similar studies have shown high microbiologic failure approaching 75% over time with mupirocin irrigations
MANUKA (LEPTOSPERNUM SCOPARIUM) HONEY

• Origin: New Zealand

• Non-toxic
  • No histological evidence of inflammation or epithelial injury in rabbit nasal mucosa

• Contains bactericidal methylglyoxal (MGO)
  • Eliminates 100% of planktonic isolates of MSSA, MRSA, PA
  • Eliminates 63-91% of biofilms
  • More effective than single anti-SA antibiotics

• No evidence of bacterial resistance
NVC-422: N,N-DICHLORO-2,2-DIMETHYLTAURINE

- Nonantibiotic antimicrobial (Singhal 2012)
  - Synthetic analog of compounds produced within phagocytes during oxidative burst
- Fast-acting, potent, broad-spectrum
  - Ability to decolonize S. aureus in human nasal cavity
  - Inactivates superantigens
  - No development of resistance
NVC-422: IN VIVO EFFICACY

- Sheep model of frontal sinusitis
- *S. aureus* biofilms
- Dose-dependent reduction in biomass following two irrigations with NVC-422 (Singhal 2012)
PHOTODYNAMIC THERAPY

- Methylene blue/EDTA photosensitizer (Biel 2013)
  - EDTA excited by red laser light
  - Electrons transferred to MB
  - Free radicals generated which compromise bacterial cell membrane integrity

- In vitro maxillary sinus model coated in PA or MRSA biofilm
PHOTODYNAMIC THERAPY: OUTCOMES

- Saline irrigation alone:
  - 1.3 log10 reduction MRSA
  - 0.6 log10 reduction PA

- EDTA/MB + PDT
  - 3.1 log10 (99.9%) reduction MRSA
  - 5 log10 (99.99%) reduction PA

- Photosensitizer alone or light alone no different than untreated control

- Limitations
  - No mucosal lining in model – not representative
  - Cannot assess cilia or tissue effect
NITRIC OXIDE

- Nitric oxide has a potent anti-biofilm effect

- In-dwelling nitric oxide generating catheters produced (Ren 2014)

- NO generated from nitrite substrate using electrochemical reduction

- E. coli biofilms formed in drip-flow bioreactor on catheter surface

- Catheter turned “on” for only 3 hrs each day over 3 days
NITRIC OXIDE

• L-arginine peptides formulated (Meyerhoff and Hershenson labs, University of Michigan)

• Human sinus mucosal explants grown in ALI

• NOS expression up-regulated with Cytomix (TNFα, IL1β, IFNγ)

• Peptides generate significant increase in NO

• Can this be replicated in vivo?

• Is the NO flux generated clinically significant?
BIOFILM DISRUPTION
SURFACTANTS

- Orthopedic literature
  - Surfactant could effectively strip biofilms from surface of stainless steel hardware

- Ampipathic molecules: solvent in both water and organic substrates
  1) Mucoactive: Prevent mucus adherence to epithelium and reduce mucus viscosity
  2) Bactericidal: Activity against planktonic and biofilm-associated microbes
## BABY SHAMPOO

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu (2008)</td>
<td>• Prospective trial (open label, nonrandomized)</td>
<td>• Inhibited biofilm growth</td>
<td>• Intolerable side effects in 10%</td>
</tr>
<tr>
<td></td>
<td>• 18 recalcitrant CRS patients</td>
<td>• Significant decrease in mucus thickness and post-nasal drainage</td>
<td>• Did not <em>eradicate</em> biofilm</td>
</tr>
<tr>
<td>Farag (2012)</td>
<td>• RCT with 44 CRS patients</td>
<td>• Both groups showed improved symptoms and olfactory testing</td>
<td>• No difference in outcome between groups</td>
</tr>
<tr>
<td></td>
<td>• Immediate post-op <strong>baby shampoo</strong> vs hypertonic saline</td>
<td></td>
<td>• 52% of shampoo group had side effects (vs 5% in saline group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 20% of shampoo group withdrew from study</td>
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CITRIC ACID/ZWITTERIONIC SURFACTANT (CAZS)

- Citric acid chelates calcium in Ca-ion bridges which are integral to biofilm structure
- Surfactant forces detached bridges into solution

<table>
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</thead>
<tbody>
<tr>
<td>Desrosiers (2007)</td>
<td>In vitro (anti-biofilm effects) • Hydrojet CAZS vs static CAZS vs hydrojet saline</td>
<td>• All therapies reduces bacterial counts • Hydrojet CAZS: 99.9% reduction in CFU counts and disrupted biofilm</td>
<td></td>
</tr>
<tr>
<td>Le (2008)</td>
<td>In vivo, sheep (antimicrobial effect)</td>
<td>• Single CAZS dose reduced SA biofilm by 80%</td>
<td>• Robust biofilm regrowth day 8 post-CAZS</td>
</tr>
<tr>
<td>Tamashiro (2009)</td>
<td>In vivo, rabbit (ciliotoxicity)</td>
<td></td>
<td>• CAZS denudes cilia (although they recover) • CAZS blunts cilia beat frequency for 6 days</td>
</tr>
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SINUSURF

• Proprietary surfactant

• In vitro
  • Sinusurf + 1:10 mupirocin or 1:100 gentamicin:
    • Reduction in biofilm by 83% (MRSA) and 76% (PA)
  • Mupirocin or gentamicin alone significantly less effective

• Withdrawn from market due to reports of anosmia
DISRUPTION OF QUORUM SENSING
POTENTIAL THERAPEUTIC TARGETS

• T2R38
  • Bitter taste receptor recently identified in human upper respiratory epithelium (Lee 2012)
  • Activated in response to AHL quorum-sensing molecules
  • Stimulates mucociliary clearance and innate immune response against biofilm

• AHL inhibition
  • Leads to flat, unstructured *Pseudomonas* biofilms
  • Enhances susceptibility to surfactant and antimicrobials
TOO MANY THERAPEUTIC TARGETS?

- Anti-IgE significantly more efficacious than anti-IL-5 therapy
- Suggests a role for mast cells and mast cell mediators
- Can we target mast cells AND eosinophils?
  - Siglec (sialic acid immunoglobulin-like lectins)
  - Siglec-8 critical to function of eosinophils, mast cells, basophils
  - Interruption of Siglec-8 neutralizes all three cell types (Kiwamoto 2012)