Medical Management of CRS

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Mucosal Inflammation
Type 1 Hypersensitivity
T-Cell mediated eosinophilia
Leukotriene dysfunction (Aspirin sensitive)
Local IgE mediated
Super-antigen/bacterial by-product
Environmental damage

Mucosal ulceration leads to greater infection and colonization

Active infection and bacterial products drive inflammatory response

Local microbial community
Bacterial planktonic
Bacterial biofilm
Fungal
Viral

Failure of mechanical & innate immune protection.
Activation of pro-inflammatory acquired immune responses

Intrinsic mucosal inflammation causes secondary mucociliary dysfunction through direct injury and mucus changes

Failure of mucus clearance leads to greater exposure to eosinophilic mucin and mucosal injury by eosinophilic mucin

Infection damages cilia and their function

Poor or absent mucociliary function fails to protect mucosa from colonization

Muco-ciliary dysfunction
Direct cilia damage
Mucus rheologic distortion
Structural/genetic abnormalities
Secondary to gross oedema/ostial obstruction
Medical Therapy for CRS

- Anti-Inflammatory
  - Corticosteroids
  - Leukotriene modifiers
  - Long term macrolides
  - Aspirin desensitization

- Antimicrobial
  - Antibacterial
  - Antifungals

- Mucociliary Stimulation
  - Saline irrigations (OTC)
  - Surfactants
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Saline: Isotonic or Hypertronic?

- Isotonic (0.9%) vs Hypertonic (2.3 – 3.0%)
- Conflicting evidence regarding efficacy
- Pooled data analysis - No significant difference
  - Transient improvement in CBF with hypertonic
  - Hypertonic (and hypotonic) possibly denude cilia
  - Hypertonic possibly better during immediate post-op period
  - Isotonic better tolerated

Saline: Irrigation or Spray?

- Comparison of saline spray vs low pressure irrigation in CRS


- Prospective RCT – 121 adult patients evaluated for 8 weeks
- Similar prescription medication profile
- Significant findings favoring irrigation group
  - Lower SNOT-20 scores at 8 weeks
  - 21% fewer patients reporting frequent symptoms
Saline: Key Points

Saline irrigation better than spray or no treatment for improving symptoms and CRS disease specific quality of life

- Mucociliary stimulation
- Natural mechanical debridement


Limited to the nasal cavity until ostial size ≥ 4mm

Surfactants

• Commercially produced
  • Detergents, soil wetting agents, paints, antifogging solutions, ski wax, toothpaste, soap
• Best known clinical example – pulmonary (acute respiratory distress of newborn)
  • Improves mucociliary clearance via reduction of mucus adhesiveness (rheology)
• Applied topically (via saline irrigation)
Answer:
The combination of PEG-80 sorbitan laurate, cocamidopropyl betaine, and sodium trideceth sulfate
What is Baby Shampoo?

• 1% optimal concentration for inhibition of Pseudomonas biofilm *in vitro*
• 2/18 (11%) d/c due to irritation
• Frequency of improvement in:
  • Overall symptoms: 46.6%
  • Thickened and postnasal drainage: 60%

Chiu et al AJR 2008
Optimized Surfactant Solution

• Removal of hair-specific ingredients, such as thickeners and fragrances
• Addition of a humectant and optimization of mucoactive ingredients
• Removed from market due to rare reported olfactory loss
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Intranasal Topical Steroids

- Onset of action – 3 - 7 Days
- Well tolerated
- Side effects: dryness, burning, epistaxis
- Maximize efficacy
  - Avoid intranasal trauma
  - Sniffing is unnecessary
  - Discuss necessity of AND verify daily use
  - Give refills
Bioavailability

Saline + Corticosteroid

- 26 patients, age 8-15 yrs with mod/severe perennial AR
- 12 week randomized study
- **Saline improves efficacy of intranasal steroid spray**

*Fig. 1. Average symptom scores of AR patients demonstrate that steroid + saline treatment improves the efficacy of treating AR in children. Data are expressed as mean ± SE. *p < 0.05, compared with steroid alone patients and saline alone patients.*
Oral Steroids

- Potent anti-inflammatory
- Short course with taper
- Potential daily dosing in disease states
  - Autoimmune disease
  - Severe asthma / atopy
  - Severe recalcitrant symptomatic inflammation
- Alternate days when possible
- Bone scan, eye exams, vit D for chronic / frequent use
Oral Steroid Side Effects - Counseling

Fluid and electrolyte disturbances: sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss, hypokalemic alkalosis; hypertension.

Musculoskeletal: muscle weakness; steroid myopathy; osteoporosis; vertebral compression fractures; aseptic necrosis; pathologic fractures; loss of muscle mass; tendon rupture - particularly of the Achilles tendon.

Gastrointestinal: peptic ulceration with possible perforation and hemorrhage; gastric hemorrhage; pancreatitis; esophagitis; perforation of the bowel.

Dermatologic: impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating.

Metabolic: negative nitrogen balance due to protein catabolism.

Neurological: increased intracranial pressure; pseudotumor cerebri; psychic derangements; seizures.

Endocrine: menstrual irregularities; development of Cushingoid state; suppression of pituitary/adrenal axis; decreased glucose tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes; suppression of growth in children.

Ophthalmic: posterior subcapsular cataracts; increased intraocular pressure; exophthalmos; glaucoma.

Immune System: masking of infections; latent infections becoming active; opportunistic infections; hypersensitivity reactions including anaphylaxis; may suppress reactions to skin tests.

Increases in ALT, AST and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.
Emotional disturbance
Enlarged sella turcica
Moon facies
Osteoporosis
Cardiac hypertrophy (hypertension)
Buffalo hump
Obesity
Adrenal tumor or hyperplasia
Thin, wrinkled skin
Abdominal striae
Amenorrhea
Muscle weakness
Purpura
Skin ulcers (poor wound healing)
### Equivalent Dosing

<table>
<thead>
<tr>
<th>Name</th>
<th>Equivalent Dose (mg)</th>
<th>Relative Anti-Inflammatory Effect</th>
<th>Relative Mineralocorticoid Effect</th>
<th>Biologic Half-Life (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.8</td>
<td>2</td>
<td>8-12</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>2</td>
<td>8-12</td>
</tr>
<tr>
<td><strong>Intermediate Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>18-36</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>18-36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>18-36</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>18-36</td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.60</td>
<td>20-30</td>
<td>0</td>
<td>36-54</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>20-30</td>
<td>0</td>
<td>36-54</td>
</tr>
</tbody>
</table>

Nasacort (triamcinolone acetonide) = 55 mcg/spray
4 sprays = 220 mcg / 5000 mcg = 4.5%
Topical Steroid Irrigation

- Nasal steroid spray (once daily dosing)
  - Nasonex 50 mcg / spray = 200 mcg/day
  - Rhinocort 32 mcg / spray = 128 mcg/day
- Steroid irrigations BID (surgery pre-requisite)
  Mometasone 0.6 mg = 1200 mcg/day (6X)
  Budesonide 0.5 mg = 1000 mcg/day (8X)
Topical Steroid Irrigation: Safety Data

- Safety (and efficacy) of budesonide in saline sinonasal irrigations in the management of chronic rhinosinusitis with polyposis: lack of significant adrenal suppression.

- No effect on serum or 24 hour urine cortisol
Low Dose Macrolide

• Proposed mechanisms

1. Anti-inflammatory (neutrophils, IL-8, IL-1b, TGF-β, TNF-α, NF-κB, NO)
2. Stimulation of ciliary motility / improves rheologic properties of mucus
3. Prevention of biofilm adhesion – quorum sensing
Macrolides: In vivo studies

Long-term low dose macrolide therapy in CRS (Cervin at al. Otolaryngol Head Neck Surg. 2002;126:481-

• 17 pts with CRS received 250 mg daily biaxin
• 12/17 responders @ 3 mos, continued x 12 mos
• VAS, saccharine transit time improved
• Open label, no placebo arm
Macrolide - Level 1b evidence

Double blind, randomized, placebo controlled trial (n=64)

- Low dose roxithromycin 150 mg qd vs placebo for 12 weeks
- Subjective and objective measures improved at 12 weeks
- Reduction in IL-8 levels (neutrophil chemotactic)
- SNOT-20 scores faded 12 weeks after treatment
- High IgE predictive of poor response

Wallwork et al. Laryngoscope 2006;116:189-193
Leukotrienes

Cyclooxygenase Pathway
Thromboxane (TX)
Prostaglandins (PG)

5-Lipoxygenase (5-LO) Pathway
5-LO enzyme + 5-LO activating protein (FLAP)

Arachidonic acid

Leukotriene (LT) A₄

5-LO inhibitor
ZILEUTON

Cysteinyi LT₁ receptor antagonists
MONTELUKAST, ZAFIRLUKAST, PRANLUKAST

Neutrophil chemotaxis and mucus production

Allergy, bronchoconstriction and mucus production

Source: Semin Respir Crit Care Med © 2002 Thieme Medical Publishers
Montelukast (Singulair)

- FDA approved for asthma, allergic rhinitis
- Little data in CRS
  - LTs chemotactic for eosinophils
  - LT production increased by activated eosinophils
- CRS w/ eosinophilic polyps + allergy / asthma
- Dose 10 mg daily
Longitudinal cohort study (n=20)

- 20 patients with CRS, asthma, nasal polyps on inhaled corticosteroid (45% allergy, 40% AERD)
- Nasal steroid + montelukast daily for 1 year
- Outcomes at 6 and durable at 12 months:
  - Reduced polyp size
  - Reduced CT score
  - Reduced peripheral eosinophilia
- Disadvantage: No comparison, no subjective

Aspirin-Exacerbated Respiratory Disease (AERD)

- Adult onset ASA sensitivity, asthma, nasal polyps (Samter’s triad)
- Metabolic shift to LT pathway
- NOT IgE mediated
  - Aspirin inhibits COX
- Dx by oral provocation
- ~50% have steroid dependent asthma
Aspirin Desensitization

- Inpatient Admission
  - Day 1 – 30 mg, escalating 30 mg q3h x 3
  - Day 2 – 100 mg, then 325 mg, then 650 mg each 3 hours apart
  - Maintenance 650-1300 mg/day
- Downregulates LT synthesis
- Improves control of polyps
- 75% have improvement in nasal symptoms
Cystic Fibrosis

- CFTR (ΔF508)
- >90% of CF patients have CRS
- 50% of carriers may develop CRS
  - Adulthood diagnosis
- Role of LTB4
  - Trials of singulair no significant efficacy
  - Zileuton?
Zileuton (Zyflo)

- 5-lipo-oxygenase inhibitor
- 1200 mg bid
- LFT monitoring: *Every month* x 3 months, then q3 months
- AERD, CF, steroid-dependent asthma
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Antibiotics

BIOFILMS

**Adverse Effects**

- Antibiotics account for a majority of drug allergy entries

- Side effects in 15-40%
  - Potential change in treatment
  - Nausea, vomiting, diarrhea, abdominal pain, headache, photosensitivity, skin rash most common
  - Severe side effects
Empiric vs Directed Therapy
Biofilms

- “Surface-associated communities of microorganisms encased in a protective extracellular matrix”
- Survival advantage
  - Avoidance of antibiotics and host defenses
  - Decreased nutrient / O2 requirements
  - Plasmid DNA sharing
Treatment Approach

• Mechanical disruption
  • Saline
  • Surfactant

• Antimicrobial treatment
  • Oral or TOPICAL

• Prevention
  • Anti-inflammatory treatment
  • Saline
  • Surfactant
Mupirocin (Pseudomonic acid)

- Produced by *Pseudomonas fluorescens*
- Mechanism of action – Inhibition of isoleucine t-RNA synthetase
- Normally administered topically
- Activity spectrum
  - Gram + (MRSA), some Gram -
Mupirocin Irrigations for MRSA
Solares et al 2006

- Treatments:
  - Mupirocin 22g 2% ointment/1L @ 50 mL bid each side 4-6 wks;
  - Alone or in combo with TMP/SMX DS or Doxycycline x 4 weeks
- Repeat culture
  - 12 not cultured due to resolution of discharge
  - 1 positive for MRSA
  - 8 positive for other organisms
Prospective, open label, n=16, +S. aureus 0.05% (500 µg/mL) bid each side x 3 weeks

TABLE I.
Summary of Symptom and Endoscopy Score Pre- and Postmupirocin Treatment in 16 Treatment Resistant CRS Patients.

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment Median Score (Interquartile Range)</th>
<th>Posttreatment Median Score (Interquartile Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analogue score</td>
<td>32.5 (23.5–38.5)</td>
<td>19 (11.5–27)</td>
</tr>
<tr>
<td>SNOT 20 score</td>
<td>45.50 (21.5–65.5)</td>
<td>30.50 (17.0–43.5)</td>
</tr>
<tr>
<td>Endoscopy score</td>
<td>8.0 (7.5–12.5)</td>
<td>3.0 (1.5–5.0)</td>
</tr>
</tbody>
</table>

CRS = chronic rhinosinusitis; SNOT = Sinonasal Outcome Test.
Mupirocin is effective against *S. aureus* biofilm *in vitro*
Ha et al Laryngoscope 2008

- Microtiter well inoculation of antibiotic solution
  - Mupirocin, ciprofloxacin, vancomycin
- MIB 50/90 (minimum biofilm inhibition concentration)
- 24 hours:
  Mupirocin MIB90 125 µg/mL or less for all isolates

### TABLE III.
Susceptibility of *Staphylococcus aureus* Isolates to Antibiotics after 24 Hours Incubation.

<table>
<thead>
<tr>
<th>Isolate Strain</th>
<th>Mupirocin</th>
<th>Ciprofloxacin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIB50</td>
<td>MIB90</td>
<td>MIB50</td>
</tr>
<tr>
<td>ATCC</td>
<td>≤7.81</td>
<td>≤7.81</td>
<td>≤7.81</td>
</tr>
<tr>
<td>1001</td>
<td>≤7.81</td>
<td>≤7.81</td>
<td>15.62</td>
</tr>
<tr>
<td>1004</td>
<td>31.25</td>
<td>125</td>
<td>≤7.81</td>
</tr>
<tr>
<td>1014</td>
<td>≤7.81</td>
<td>62.5</td>
<td>≤7.81</td>
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<tr>
<td>1015</td>
<td>≤7.81</td>
<td>15.62</td>
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<td>1019</td>
<td>15.62</td>
<td>62.5</td>
<td>≤7.81</td>
</tr>
<tr>
<td>1081</td>
<td>15.62</td>
<td>31.25</td>
<td>≤7.81</td>
</tr>
<tr>
<td>1063</td>
<td>≤7.81</td>
<td>≤7.81</td>
<td>≤7.81</td>
</tr>
<tr>
<td>1080</td>
<td>≤7.81</td>
<td>62.5</td>
<td>≤7.81</td>
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*Values are numbers of micrograms per millimeter.*
*ATCC = American Type Culture Collection; MIB50/90 = minimum biofilm inhibition concentrations at 50% and 90%.*
Mupirocin: Sheep Model *in vivo*

- 54 frontal sinuses inoculated w/ Staphylococcus biofilms
- Control biofilm surface area coverage 31.7%
- Day 8 surface area coverage (after 5 days of bid flushes):
  - Saline wash 23%
  - Mupirocin 0.84% (lowest of all regimens tested)

Le et al AJR 2008
Case Example

- 17 yo male with CRS, s/p adenoid/ESS
- Allergic negative, Ig subclasses normal
- Culture – MRSA
- Meds: Nasal steroid, oral antihistamine
- Treatments – oral abx (C diff), oral steroids, mupirocin irrigations

Right middle meatus  Left middle meatus  Nasopharynx
Right middle meatus

Left middle meatus

Nasopharynx

Treatment
Tobramycin

- Aminoglycoside (broad spectrum)
  - Typical IV dose: 1.5-2.5 mg/kg q8-12h
    (180 mg/60kg if q12h)
  - Irrigation dose: 40 mg / 100 mL
- Efficacy demonstrated in CF patients
- Risk of ototoxicity
  - Middle ear penetration
  - Systemic absorption
  - Mitochondrial 12S RNA mutations 15%
Antifungal Agents
Where’s the evidence....

SinuNase™ has not yet been approved by the U.S. FDA or any international regulatory agency, and this product is likely to require additional clinical trials before potential approvals are granted.
Allergic Fungal Sinusitis

- Allergic reaction to aerosolized environmental fungi in immunocompetent
- Immunologic rather than infectious
- Possible role for antifungals
  - Positive culture
  - Anecdotal results
  - Poor response of dermatiaceous fungi
  - Avoid oral/IV
Manuka Honey

- 100% effective at killing planktonic bacteria
  - Biofilms – pseudomonas 91%, staph 63-82%
  
  Alandejani et al Otolaryngol Head Neck Surg 2009

- No histological effect on respiratory epithelium or cilia in rabbit model

  Kilty et al Am J Rhinol Allergy 2010

- Methylglyoxal is biofilm-cidal in vitro

  Jervis-Bardy J et al Laryngoscope 2011
Symptoms of CRS

- Topical Steroid + / - Saline Irrigations Antihistamine Antibiotic
- Nasal Endoscopy + / - CT Scan
  - Referral
  - Inadequate control
- Oral Steroid + / - Antibiotic
  - Inadequate control
  - Referral
- Treat Exacerbations Identify Causes Medication Trials
  - Inadequate control
- Endoscopic Sinus Surgery
  - Inadequate control
  - Exception
  - Positive Findings
Conclusions

• CRS is a complex interplay between inflammation, microbial community, and mucociliary dysfunction

• Medical treatment is the mainstay, even after surgery

• Therapy is individual / driven by etiology and objective findings