Update on Chronic Rhinosinusitis- The more we know, the less we know??

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AOCCOO-HNS
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Presenter and Disclosures

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• Residency- MSUCOM Statewide Campus-McLaren Oakland
• Fellowship- Sinus and Nasal Institute of Florida- Donald C. Lanza M.D.
• Lakeshore Ear, Nose, Throat Center PC
• Disclosures
  • NONE
Objectives

• Define CRS- Do we have it right?
• What’s maximum medical therapy?
• Irrigation
• Discuss the human genome project- sinus
• Discuss culture directed antimicrobial therapy: Then- Now
• Chronic Nasopharyngitis
Definition

• 2004
  • Chronic rhinosinusitis is a multifactorial disease defined as inflammation of the nasal cavity and sinuses with a history of at least 12 weeks duration. Major symptoms of facial pressure/pain, nasal obstruction, discharge or purulence, and hyposmia. Minor-fever, halitosis, fatigue, and dental pain. Microorganisms play a significant role in persistence and origination of the inflammatory process, although the exact role of these organisms in the pathogenesis of CRS is unclear.
Definition

“Rhinosinusitis is defined as *symptomatic* inflammation of the paranasal sinuses and nasal cavity. The term rhinosinusitis is preferred because sinusitis is almost always accompanied by inflammation of the contiguous nasal mucosa.”

- Is all sinusitis symptomatic??
- Many chronic sinusitis patients can have active infection and or inflammation in the paranasal sinuses without any symptoms.

Maximal Medical Therapy?

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Anti-IgE Anti IL-5</th>
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<tr>
<td>Antimicrobials</td>
<td>Immunotherapy</td>
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<td>Nasal lavage</td>
<td>Mucolytics</td>
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<td>Antihistamines</td>
<td>Decongestants</td>
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<td>Leukotriene modifier</td>
<td>Smoking cessation</td>
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Maximal Medical Therapy

- As definition states CRS is product of inflammation
- Goal of medical therapy is to reduce inflammation
- Not all inflammatory responses are the same and best understanding of underlying condition leads to best medicine
What’s the Immune Status

- Allergies
- Immunodeficiency
- Cystic fibrosis
- Kartagener’s
- Dentition
Steroids and antibiotics

Oral steroids and doxycycline: two different approaches to treat nasal polyps.

In a double-blind, placebo-controlled, multicenter trial, we randomly assigned 47 participants with bilateral nasal polyps to receive either methylprednisolone in decreasing doses (32-8 mg once daily), doxycycline (200 mg on the first day, followed by 100 mg once daily), or placebo for 20 days. Participants were followed for 12 weeks. Patients were assessed for nasal peak inspiratory flow and symptoms and by nasal endoscopy. Markers of inflammation such as eosinophilic cationic protein (ECP), IL-5, myeloperoxidase, matrix metalloproteinase 9, and IgE were measured in nasal secretions. Concentrations of eosinophils, ECP, and soluble IL-5 receptor alpha were measured in peripheral blood samples.

RESULTS:
Methylprednisolone and doxycycline each significantly decreased nasal polyp size compared with placebo. The effect of methylprednisolone was maximal at week 3 and lasted until week 8, whereas the effect of doxycycline was moderate but present for 12 weeks. Methylprednisolone significantly reduced levels of ECP, IL-5, and IgE in nasal secretions, whereas doxycycline significantly reduced levels of myeloperoxidase, ECP, and matrix metalloproteinase 9 in nasal secretions.

CONCLUSION:
This is the first double-blind, placebo-controlled study to show a significant effect of oral methylprednisolone and doxycycline on size of nasal polyps, nasal symptoms, and mucosal and systemic markers of inflammation.

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• Double blind, parallel group, randomized study aimed at evaluating the clinical and anti-inflammatory effects exerted by either of two different antihistamines (Claritin and Clarinex) plus montelukast in patients with SAR and mild intermittent asthma

- Combinations significantly reduced:
  - Nasal symptoms (p<0.001)
  - Eosinophils and neutrophils (p<0.001)
  - IL5 (p<0.001 for M-C group and p<0.01 for M-D group)
  - IL8 levels (p<0.001 for M-C group and p<0.05 for M-D group)
Urinary Cysteinyl-Leukotrienes after surgery

- J Allergy Clin Immunol. 2004 Feb;113(2):277-83
- Higashi N et al.
- Clinical features of asthmatic patients with increased urinary leukotriene E4 excretion (hyperleukotriienuria): Involvement of chronic hyperplastic rhinosinusitis with nasal polyposis.
Urinary Cysteinyl-Leukotrienes Before and After Surgery in ASA and Non-ASA Sensitive Patients

• Significant decreases in the U-LTE4 concentrations before and after the sinus surgery in both AIA and ATA groups (p<0.05)

• Conclusion: Cysteiny l leukotrienes are not strictly associated with aspirin intolerance itself but rather with clinical features such as CHRS/NP, that are similar to those seen in AIA. CHRS/NP might be involved in cysteinyl leukotriene overproduction in asthmatic patients.
Irrigation

• Int Fourm Allergy Rhino 2013. Sept 3:708-11
• Budesonide nasal irrigation in the postoperative management of chronic rhinosinusitis
• Jang DW, Lachanas VA, Segel J, Kountakis SE
Irrigations

• Retrospective review of prospective data.
• 60 patients given budesonide after surgery but had a lapse in treatment of at least 1 month. Compared SNOT-20 and Lund-Kennedy scores when patient on budesonide vs off.
• 30 pts with eCRSwNP, 13 AFS, 13 Samters, 4 eCRSsNP followed for 25 months
• Overall SNOT-20 significantly lower with budesonide (p<0.05) with endoscopy only improved in the eCRS group
Irrigation

- Am J Rhinol Allergy 2013. May-Jun 27(3):221-33
- Sinus surgery and delivery method influence on the effectiveness of topical corticosteroids in rhinosinusitis: systematic review and meta-analysis
Irrigations

- Systematic review of RCT’s comparing INCS with placebo or no intervention and broken down for surgery status and delivery methods
- 48 studies with (3961 pts)
- INCS improved overall symptoms compared placebo ($p<0.00001$)
- Decreased nasal polyp ($p<0.00001$) and prevented recurrence ($p<0.0004$) compared placebo
- Reduction in polyp size greater in those with sinus surgery than without
- Greater symptom improvement in delivery method of sinus delivery (lavage) compared to nasal (spray)
Nose is not sterile

- Significant contribution to this belief from the research done in the Human Microbiome Project suggesting cohabitation of “normal flora” for certain body sites


- Middle meatal swabs of 28 consecutive patients with NO signs or symptoms of rhinosinusitis evaluated with PCR and 16S rRNA sequencing

- Staphylococcus epidermidis (96.4%), propionibacterium acnes (92.9%), Staphylococcus aureus (67.9%) most common

- Relative abundance 11%, 14.7%, 8.3%
Microbial DNA Sequencing

- Clinical identification of bacteria in chronic wound infections: culturing vs 16s ribosomal DNA sequencing
- Rhoads DD, Cox SB, Rees EJ, Sun Y, Wolcott RD
- Parallel sampling standard culture and DNA
- Study set the table for suggesting that DNA sequencing can detect a greater number of pathogens than standard culture techniques and can indicate relative abundance which may hint a pathogenicity
Microbial DNA Sequencing and CRS Flora

- What bacteria represent “normal flora” in a CRS

- Prior studies suggest CRS pathogens more commonly Staphylococcus a. and coagulase negative Staphylococcus which differs from that of acute bacterial sinusitis.

- Discrepancy between standard agar plating culture mediums and DNA sequencing.

- Does this play a role in refractory nature of CRS even with culture directed antibiotics.

Microbial DNA Sequencing and CRS Flora

- Prospective study 18 pts for surgery with CRS vs 9 controls (surgery PA).

- Interestingly standard cultures revealed Coag neg staph (53%) and staph a. (18%)

- CRS DNA sequencing 3 most common were anaerobes
  - Propionibacterium (83 %)
  - Diaphorobacter (78%)
  - Peptoniphilus (72%)
  - Corynebacterium (61%)
Microbial DNA Sequencing and CRS Flora

• 9 Controls
  • Staphylococcus a
  • Corynebacterium
  • Propionibacterium

• Questions
  • Are anaerobes a larger source of pathogenicity in CRS
  • If so, is current gold standard of culture techniques appropriate
Pathogenius™

- To compare commercially available DNA technology to standard culture techniques
- 204 total patients
  - 120 aerobic, anaerobic, fungal and DNA
  - 94 aerobic, fungal and DNA
- Showed similar results with respect to increased bacterial and fungal pathogens identified.
- All cultures with no growth in standard medium produced pathogens on DNA sequencing
Mean # Microbes Detected
SSCULT vs. DNA Probe

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<thead>
<tr>
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<th>SSCULT</th>
<th>DNA Probe</th>
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</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>1.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Fungus</td>
<td>0.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Antibiotic Resistance Detected
SSCULT vs. DNA Probe

# Specimens with Resistance

Methicillin  Quinolone

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<tr>
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<th>DNA Probe</th>
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<tbody>
<tr>
<td>Methicillin</td>
<td>10.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Quinolone</td>
<td>30.0</td>
<td>20.0</td>
</tr>
</tbody>
</table>
Bacteria Detected By DNA Analysis When "No Growth" or "Normal Flora"

- **S. epidermidis**: 7 specimens
- **P. aeruginosa**: 4 specimens
- **S. Aureus**: 3 specimens
- **S. Maltophilia**: 2 specimens
- **Corynebacterium**: 2 specimens

# Specimens
Pathogenius

• Limitations
  • Currently there is no commercial marker for quinolone resistance which can create challenges particularly with Pseudomonas
  • Cost

• Theoretical benefit
  • Refractory cases of CRS additional bioburden identification may lead to a medical treatment change
  • However, as previously stated mere presence in the sinus or nasal cavity doesn’t confer pathogenicity.
Chronic Nasopharyngitis

• Recognizable CPT code- 472.2
• Theorize that this may represent a subset of patients who are “misdiagnosed” as acute bacterial sinusitis or even chronic rhinosinusitis
• Paucity of literature regarding this topic
• Preliminary research seems to indicate that there are a separate subset of symptoms and perhaps refractory nature of treatment.
CNP Examples
Chronic Nasopharyngitis-CRS Masquerader

• If you don’t know what to look for you don’t know what to look for

• Potential treatments
  • GERD
  • Rinsing
  • Antimicrobials-Topical and oral
  • Surgery- cautery
Chronic Nasopharyngitis

- Retrospective chart review with 12 patients
- All 12 with complaint of post nasal drip with (10/12) nasal congestion, (7/12) cough, (7/12) auricular fullness.
- 5/12 with history of indigestion, heartburn or reflux
- Staphylococcus aureus most common culture
- Variety of treatments including saline lavage, oral and topical antibiotics, PPI’s all with varying results
- Bartely and Barber in 2010 N of 4 with CNP treatment with unipolar cautery with improvement or resolution in all 4.