Medical Management of Chronic Rhinosinusitis

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Outline

- Anatomy, epidemiology & definition
- Diagnosis
- Predisposing factors
- Role of allergy
- Treatment strategies
  - Etiology
  - Inflammatory response
Anatomy of the sinus

Osteomeatal Complex
Rhinosinusitis
Epidemiology

- Affects 14% of the U.S. adults (national census data)
- The American Academy of Otolaryngology (AAO) reports a direct health care costs of $3.4 billion / year
- Top ten diagnosis associated with loss of productivity
- 18 to 22 million US physician office visits annually
Rhinosinusitis Definition

- AAO definition - Defined as an inflammation of the nose and sinuses
- *Rhinosinusitis*
  - Include nasal airway inflammation (Rhinitis)
Rhinosinusitis Symptoms

- A rhinosinusitis task force in 1997
- "major" criteria
  - facial pain
  - nasal obstruction
  - Hyposmia
  - purulence on examination
  - fever
- "minor" criteria
  - Headache
  - Fatigue
  - dental pain
  - cough
Classification by Duration of Symptoms

- **ACUTE** – lasting up to 4 weeks, with total resolution of symptoms

- **SUBACUTE** – persisting more than 4 weeks, but less than 12 weeks, with total resolution of symptoms

- **CHRONIC** – 12 weeks or more of signs / symptoms

- **RECURRENT ACUTE** – 4 or more episodes per year, with resolution of symptoms between attacks
Chronic rhinosinusitis (CRS)

- Symptom-based diagnosis may be unreliable
- Patient with “sinus all the time,” chronic headache and facial “pressure,” plus “stopped up” nose; has had “innumerable” courses of antibiotics and 3 sinus operations by 2 different physicians
- Computed tomography is the gold standard
Predisposing Factors In Chronic rhinosinusitis (CRS)

- **Host Factors**
  - **Systemic**
    - Allergic rhinitis
    - Immunodeficiency
      - IgG subclasses
      - IgA
    - Genetic/congenital
      - cystic fibrosis, ciliary dyskinesia
  - **Local**
    - Anatomic obstruction
    - Gastroesophageal reflux

- **Enviromental factors**
  - Microorganisms
    - viral illness (children in daycare)
  - Pollutants
    - cigarette smoke
  - Medications
    - Rhinitis medicamentosa
Possible Strategies for Treating CRS

**Treat Etiology**
- Allergen Avoidance
- Antibiotics
- Surgery

**Attenuate Inflammation**
- Steroids
- Immunotherapy
- Antileukotrienes
- Macrolides
- Who knows what else?

**Infectious**
- IL-5, IL-4
- IL-8, IF-\(\gamma\)
- GM-CSF

**Anatomic**
Sinus ventilation and drainage

- Oral hydration
- Saline sprays
- Humidification
- Decongestants
- Mucolytics
**Allergies in CRS**

- Most common predisposing factor in adults
- Second most common in children (after viral URI)
- Allergic rhinitis leads to mucosal inflammation and hypertrophy blocking the ostiomeatal complex
Management of allergies

- Allergen avoidance
  - history or positive skin prick tests
- Saline irrigation
- Antiinflammatory therapy
- Antihistamine
- *Leukotriene Receptor Antagonists*
- Decongestant
Saline irrigation

- Increase mucociliary flow rates
- Brief vasoconstrictive effect
- Mechanically rinse
- Adding baking soda
  - Alkaline medium leads to thinning of mucus
  - An acidic medium creates a more viscous (gel) mucus
Mucolytics

- Guaifenesin
  - High doses are required for obtaining an effect on mucous
    - Emesis and abdominal pain
- Wawrose 1992
  - Significant improvement of nasal congestion in patients with AIDS and low CD4 counts
Antihistamine

- Inhibition of histamine receptor
- Ineffective in relieving chronic nasal congestion
- First-generation antihistamines
  - Anticholinergic
    - adverse effects such as drowsiness
    - Leads to drying of secretions
Second-generation antihistamines

- Higher affinity to histamine receptors and increased potency
- No anticholinergic effect
- Cetirizine
  - Block other mediator release such as that of leukotrienes and kinins
  - Inhibit monocyte and lymphocyte chemotaxis
  - Beneficial in the treatment of chronic congestion
Leukotriene

- More potent than histamine in triggering nasal allergic inflammation

- *Leukotriene Receptor Antagonists*
  - Effective in allergic rhinitis
  - Beneficial effects for the indication of chronic rhinosinusitis
Corticosteroid

- **Inmunomodulator**
  - Stabilize mast cells
  - Block formation of inflammatory mediators
  - Inhibit chemotaxis of inflammatory cells

- **Short courses of systemic corticosteroids**
  - Tx severe nasal mucosal congestion in allergic patients
Corticosteroid

- Contraindications
  - Diabetes
  - Peptic ulcer disease
  - Glaucoma
  - Severe hypertension
  - Advanced osteoporosis
Topical corticosteroids

- Improve patency of the ostiomeatal complex
  - reduction in mucosal swelling
- Inhibit both immediate and late-phase reactions to antigenic stimulation (After 7 days of treatment)
- 90% of patients with allergic rhinitis will experience improvement
Topical corticosteroids

- Common adverse effects
  - nasal irritation, mucosal bleeding, and crusting
  - propylene glycol contained in the preparations

- Alleviated by switching to a aqueous delivery system

- Concomitant nasal saline used lessen or eliminate the adverse effects
Decongestants

- vasoconstriction of dilated mucosal blood vessels (α-adrenergic agonists)
- symptomatic relief of nasal congestion
- No therapeutic efficacy for the treatment of sinusitis
Topical Decongestants

- Phenylephrine & oxymetazoline
- Rhinometric analysis
  - Rebound vasodilation as early as 3 days
- Rhinitis medicamentosa
  - after 10 days to 2 weeks
Antibiotics in CRS

- Should be based on culture results
- Endoscopic directed culture of purulent secretions from the nasal vestibule or middle meatus correlate well with maxillary tap results
- S. aureus, Anaerobes & Gram negative
- Pseudomona Aeruginosa
Antibiotics

- **First-line**
  - amoxicillin-clavulanate
  - cephalosporin second- or third-generation

- **Second-line**
  - For adults
  - The respiratory quinolones
    - ciprofloxin, levofloxacin, gatifloxacin, and moxifloxacin
Antibiotics

- Additional and backup
  - Clarithromycin and azithromycin achieve excellent mucosal levels
  - Pneumococcal resistance to macrolides double over the past 10 years from approximately 10% to 20%
  - Clindamycin should be reserved for culture-documented resistant *S. pneumoniae*
Duration of antibiotic

- Broad-spectrum antibiotic for up to 3 weeks.
  - Improvement in symptoms within 3 to 5 days.
  - Resolution of symptoms within 7 to 10 days after first improvement.
  - Another week- to diminish mucosal edema and improve mucociliary function

- Rapid recurrence after previous treatment
  - Add 3- to 6-week course of once-daily prophylactic antibiotic therapy
Mechanisms of Antibiotic Resistance or "Bugs are smarter than us"

- **H. influenzae**
- **M. catarrhalis**
- **S. pneumoniae**

**BACTERIAL CELL**

- DNA
- ENZYME PRODUCTION (β-lactamase)
- EFFLUX
- ALTERED TARGET PROTEINS
- RIBOSOMES

**ALTERNED PENICILLIN BINDING PROTEINS**

- Macrolides
- β-lactams
- Quinolones
Macrolide

- Antiinflammatory effect
- Accumulate in inflammatory cells
  >100X higher than concentrations in extracellular fluid
Macrolide
Immunomodulator effect

- Macrolide antibiotics targets cytokine production
  - Decreased IL-5, IL-8, GM-CSF, TGF-β, IL-6, IL-8, TNF-α
- Altered structure and function of biofilm
- Reduced expression leukocyte adhesion molecules
- Accelerate neutrophil apoptosis
- Impaired neutrophil oxidative burst
- Decrease secretion and improve mucociliary clearance
- Inhibited release of elastase, protease, phospholipase C, and eotaxin A by *P aeruginosa*
Macrolide

- Long-term, low-dose macrolides for treatment of CRS (primarily in Japan)
- Clarithromycin is the macrolide most studied in CRS
- Azithromycin lack studies in CRS
- Long term use is 3-12 month
Meta-analysis of macrolides in Chronic rhinosinusitis

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Dosage 24h (mg)</th>
<th>Duration (months)</th>
<th>Macrolide</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, randomized, controlled trial, n = 90</td>
<td>1000 (2 wk)</td>
<td>3</td>
<td>Clarithromycin</td>
<td>As effective as surgery in chronic sinusitis</td>
<td>Ragab, 2004</td>
</tr>
<tr>
<td></td>
<td>500 (10 wk)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prospective, open, n = 17</td>
<td>500</td>
<td>12</td>
<td>Erythromycin</td>
<td>12 responders, mucociliary transport, headache, postnasal drip, all improved, $P &lt; .05$</td>
<td>Cervin, 2002</td>
</tr>
<tr>
<td>Prospective, open, n = 20</td>
<td>1000</td>
<td>0.5</td>
<td>Clarithromycin</td>
<td>Improvement in CD68, IL-6, IL-8, TNF-α and clinical parameters</td>
<td>Macleod, 2001</td>
</tr>
<tr>
<td>Prospective, open, n = 20</td>
<td>400</td>
<td>3</td>
<td>Clarithromycin</td>
<td>Reduction of IL-8 in nasal lavage, decreased nasal polyp size</td>
<td>Yamada, 2000</td>
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Cervin et al. 2005
GERD in CRS

- Reflux reach the nasopharynx and nasal cavities leading to chronic mucosal irritation and sinusitis
- Adult patients with chronic sinusitis and a history of heartburn
  - antireflux regimen –precaution and med
- Young children the relation is more evident
  - presumably due to the closer proximity between the esophageal inlet and larynx to the soft palate and nasopharynx
  - suspected in children
    - chronic congestion
    - Rhinorrhea
    - excessive spitting up in infancy
    - low weight percentile
    - failure to thrive
    - chronic stridor
    - reactive airway disease
Viral infections

- Most common predisposing factors for sinusitis in children
- Day care important risk
  - fewest possible children to reduce viral exposure
- Prevention
  - Hand washing
- IFN a2 ($$$$$)
Conclusion

- CRS is multifactorial
- Treatment is based on pt’s predisposing factors
- Therapeutic options
  - Prevent & treat etiology
  - Reduce inflammatory response
- Surgery
  - Exhaustion of medical option
  - Certainty of diagnosis