“SINUSITIS: WHAT’S NEW, WHAT’S OLD”

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Objectives

- Briefly review the anatomy and physiology of the paranasal sinuses.
- To define the accepted diagnostic criteria for rhinosinusitis.
- To understand the treatment of sinusitis in terms of its proposed etiology.
- To describe different antibiotic classes, mechanisms activity, and patterns of resistance.
- To understand various adjunctive medications and their usefulness, including newer treatments such as antifungal medications and nebulized antibiotics.
Embryology of Nasal Cavity and Paranasal Sinuses

- Embryology
  - Series of ridges and furrows that develop along lateral nasal wall at 9th and 10th week of gestation
  - Each ridge has an ascending and descending portion
  - Ridges fuse and persist into adult life as inferior, middle and superior turbinate
  - 1st Ethmoturbinal - agger nasi region and uncinate process
  - 2nd Ethmoturbinal - middle turbinate
  - 3rd Ethmoturbinal - superior turbinate
  - 4th/5th Ethmoturbinal - supreme turbinate
Anatomy of Nasal Cavity and Paranasal Sinuses

- **Vascular anatomy**
  - Internal carotid artery via ophthalmic branches: anterior and posterior ethmoidal arteries, exterior carotid via internal maxillary and facial arteries
Physiology - Air Flow

- Nasal valve region is the flow limiting region of the nasal airway.
  - Anterior end of inferior turbinate
  - Lower lateral cartilage
  - Nasal septum

- Approximately 90% of the air flow is directed at the head of the middle turbinate

- Airflow is turbulent not lamina

- Only about 15% of the airflow reaches the olfactory area

- No flow – no smell
Physiology – Mucocilliary Clearance

- Coordinated process of the pseudostratified ciliated columnar epithelium
- Mucociliary clearance of the paranasal sinuses is a non-gravity dependent active process
- Cilia beat rapidly through the gel phase of the mucous and return slowly through the sol phase
- Mucous layer is replaced every 20-30 minutes
- Nose produces about a liter of mucous a day
Normal Sinus Health Cycle

Secretions stay fluid, contain antibodies and IgA

Ostium is Open

Particulate matter and bacteria are removed by mucociliary clearance

Mucociliary flow prevents local mucosal damage

Host defenses resist infection

Soluble pollutants are absorbed in the mucosa

Mucous composition is normal

Mucous secretion is normal

Rhinosinusitis: Burden of Illness

- Among the top 8 most common diagnosis in the ambulatory practice
- 5th for antibiotic treatment
- 3rd for over the counter medications
- 14% of U. S. adults annually say they were diagnosed with rhinosinusitis
- Costs 3.4 billion dollars per year
- Impacts quality of life and productivity
Purulent Drainage in Middle Meatus from Ethmoid / Maxillary Infection

Middle Meatal Pus
Acute Bacterial Rhinosinusitis: Diagnosis
(Requires at least two majors or one major and two minor factors)

Symptoms worsening after 5-7 days, persistence of major symptoms(s), greater than 10 days, or symptoms out of proportion with typical URI.

Symptoms

Major Factors
- Nasal/postnasal drainage*
- Facial pain/pressure*
- Nasal obstruction/congestion*
- Hyposmia/anosmia

Minor Factors
- Fever
- Cough
- Fatigue
- Maxillary dental pain
- Ear fullness/pressure
- Headache

*Most common symptoms
Types of Rhinosinusitis Based on 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

- **RECURRENT ACUTE** – 4 or more episodes per year, with resolution of symptoms between attacks

- **CHRONIC** – 12 weeks or more of signs / symptoms
CT Scans for Rhinosinusitis

- Should not be used as the sole diagnostic criteria
- Indicated for:
  - Questions of diagnosis and/or therapy
  - Strong history not responding to therapy
  - Prior to sinus surgery
- Timing of CT scan:
  - Chronic rhinosinusitis after four weeks or more of appropriate antibiotic therapy
  - Recurrent acute sinusitis in search of origin or problem
  - An acute disease if extra sinus spread of infection
  - Acute viral URI’s 87% of sinus CT’s are positive with 21% remaining so for up to 2 weeks following clinical resolution

Factors Predisposing to Bacterial RS

- **Viral URI**
  0.5–2% become bacterial in adults; 2–5% in children

- **Allergic rhinitis**
  inhalant sensitivities raise incidence 4.5X

- **Anatomic ostiomeatal obstruction**

- **Air pollution**
  smoking raises incidence (1.22X); work-related factors in cotton mills, bakeries, photo developing establishments, etc.

- **Nasal polyposis**
  Samter’s triad, AFS, inhalant / food allergies

- **Medication effects**
  rhinitis medicamentosa, cocaine, antihypertensives, BCPs, most nasally delivered topical agents

- **Other causes**
  GERD, pregnancy, immune deficiency, asthma, diabetes mellitus, maxillary dental disease, mucociliary disorders, etc.
Pathogenesis of an Upper Respiratory Infection

Virus Infection of Nasal Epithelium

Proinflammatory cytokines (IL-1, -6, -8)

Secondary inflammation (PMNs, kinins)

Vasodilation

serum transudation

Mucus secretion

Airway hyperreactivity

Neurogenic responses

Tracheobronchial infection

Cholinergic stimulation

Sore Throat

Sneezing

Nasal Obstruction

Rhinorrhea

Cough
Causes of Rhinosinusitis – Time Course

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Percent of Patients</th>
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<tbody>
<tr>
<td>0–4</td>
<td>100%</td>
</tr>
<tr>
<td>5–20</td>
<td>80%</td>
</tr>
<tr>
<td>21–60</td>
<td>40%</td>
</tr>
<tr>
<td>61–100</td>
<td>20%</td>
</tr>
<tr>
<td>101–200</td>
<td>10%</td>
</tr>
</tbody>
</table>

Viral infections dominate in the first 5–20 days, followed by resistant aerobes, anaerobes, and fungi.
Sinus Cycle Leading to Rhinosinusitis

- **Ostium is Closed**
  - Mucosal congestion (often due to viral rhinitis) or anatomic obstruction blocks airflow and drainage

- **Secretions stagnate**
  - Secretions thicken, pH changes

- **Mucosal gas metabolism changes**
  - Cilia and epithelium are damaged

- **Change in host milieu creates culture medium for bacterial growth in closed cavity**

- **Retained secretions cause tissue inflammation**

- **Bacterial infection develops in the sinus cavity**

- **Mucosal thickening creates further blockage**

Ostiomeatal Complex = Most Common Site of Sinus Obstruction
Biofilms and Rhinosinusitis

- Biofilm formation is likely present in most infections, acute and chronic
- Infection takes place on the surface of the sinus mucosa (i.e. sinus mucosa is not invaded by bacteria)
- Bacterial attachment to the mucosa is not an important etiology to the disease
- Organisms causing sinusitis appear to originate in the nasopharynx
Streptococcus pneumoniae and Haemophilus influenzae are the predominant pathogens in adults, with Moraxella catarrhalis joining such in children.

Pathogens in ABRS:
- *Staphylococcus aureus*: 0–8%
- *Anaerobes*: 0–9%
- *Other streptococci*: 3–9%
- *Moraxella catarrhalis* (peds = 21–28%)
- *Other bacteria*: 4%
- *S. Pneumoniae* (peds = 35–42%)
- *H. influenzae* (peds = 21–28%)
- *20-43%*
- *22-35%*
Rhinosinusitis: Cultures

- Nasal cultures are not routinely indicated in first-line management of acute rhinosinusitis.
- Endoscopically guided microswab or suction aspiration culture of a draining sinus ostium is a strong consideration in chronic rhinosinusitis, especially when poorly responsive to prior antibiotics.
Antibiotics Approved By The FDA For Acute Maxillary Sinusitis

- **β-lactams**
  - Amoxicillin – Clavulanate (Augmentin)
  - Cefdinir (Omnicef)
  - Cefpodoxime proxetil (Vantin)
  - Cefprozil (Cefzil)
  - Cefuroxime axetil (Ceftin)

- **Macrolides**
  - Clarithromycin (Biaxin)
  - Telithromycin (Ketek)
  - Azithromycin (Zithromax)

- **Quinolones**
  - Siprofloxacin (Cipro)
  - Gatifloxacin (Tequin)
  - Levofloxacin (Levaquin)
  - Moxifloxacin (Avelox)
Pharmacodynamic Antimicrobial Activity Patterns

- **Time dependent killing with minimal to moderate persistent effects**
  - Seen with β-lactams (penicillins, cephalosporins), clindamycin and macrolides (erythromycin, clarithromycin)
  - Goal of dosing regimens optimize **duration** of exposure
  - (Time above MIC) is a major parameter correlating with efficacy
  - Serum concentration of free drug present for greater than 40% of dosing intervals for penicillin’s and greater than 50% for cephalosporin’s predicts efficacy and determines susceptible MIC breakpoint
Pharmacologic Antimicrobial Activity Patterns

- **Concentration dependent** killing with prolonged persistent effects
  - Seen with aminoglycosides, quinolones, telithromycin
  - Goal dosage regimen to maximize exposure (amount)
  - AUC/MIC in peak concentrations/MIC are major parameters correlating with efficacy
  - AUC/MIC ratio of greater than 25 needed in immuno competent host
  - AUC/MIC ratio of greater than 125 needed in immuno compromised hosts or in severe infections
Mechanisms of Antibiotic Resistance or “Bugs are smarter than us”

- **BACTERIAL CELL DNA**
- **ALTERED PENICILLIN BINDING PROTEINS**
- **ENZYME PRODUCTION (β-lactamase)**
- **EFFLUX**
- **ALTERED TARGET PROTEINS (somerases)**
- **RIBOSOMES**
- **DNA**

- **H. influenzae**
- **M. catarrhalis**
- **S. pneumoniae**
Bacterial Resistance and Antibiotic Additives To Animal Feed

- 11.2 million kg of antibiotics to animals each year vs 1.3 million kg to humans
- 20% of the samples of ground meat obtained in supermarkets contained salmonella resistant to one or more antibiotics
- 17% of the chickens obtained in supermarkets have organisms resistant to antibiotics
  - Resistant organisms isolated from chicken parts were able to successfully colonize the bowel of healthy volunteers for up to 14 days*

Adult Chronic Rhinosinusitis

Is a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks duration.

Progression of Changes in the Nasal Mucosa in Chronic Rhinosinusitis

Courtesy of Ciba Geigy Clinical Symposia, 1989
Rhinosinusitis is a mucosal infectious disease. Swelling often the result of a viral infection which leads to obstruction, which leads to mucostasis, which leads to bacterial infection, which leads to further swelling and further obstruction and further mucostasis and becomes a self fulfilling process ultimately leading to chronic rhinosinusitis.
# Pathogenesis of CRS: Role of Bacteria

<table>
<thead>
<tr>
<th>No prior surgery</th>
<th>No prior surgery</th>
<th>Prior Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobes – 75–100%</td>
<td>Anaerobes – 0–25%</td>
<td></td>
</tr>
<tr>
<td>Coag- neg. Staphylococci</td>
<td><em>Fusobacterium</em> sp.</td>
<td><em>Pseudomonas</em> sp.</td>
</tr>
<tr>
<td><em>Staph. Aureus</em></td>
<td><em>Proventella</em> sp.</td>
<td><em>Klebsiella</em> sp.</td>
</tr>
<tr>
<td><em>Strep. Pneumonia</em></td>
<td><em>Peptostreptococcus</em> sp.</td>
<td><em>Enterobacter</em> sp.</td>
</tr>
<tr>
<td><em>Strep. viridans</em></td>
<td><em>Propionibacterium</em> sp.</td>
<td><em>Coag- neg. Staphylococci</em></td>
</tr>
<tr>
<td><em>H. Influenza</em></td>
<td></td>
<td><em>S Aureus</em></td>
</tr>
<tr>
<td><em>Corynebacterium</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
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Bone Involvement In Chronic Rhinosinusitis

- Blockage of osteomeatal complex with infected inflammed mucosa
- Bone involvement studied through histomorphometry.
  - Tetracycline bone labeling chronic rhinosinusitis patients shows marked activity in about 40%, mild activity in another 35%, similar to that seen in osteomyelitis.
  - Control patients showed marked activity in 5% and mild activity in 25%
  - Bone becomes involved with infection through bacterial involvement with mucosa
  - “Osteomyelitis” like involvement of bone

Fungal Involvement In Chronic Rhinosinusitis

- Allergic fungal sinusitis
- All chronic rhinosinusitis is fungal sinusitis
  - Fungal cultures are positive in virtually all cases of chronic rhinosinusitis where special techniques are utilized
- Allergic mucin is found in greater than 98% of the surgical cases
- Fungal isolation is not successful in over half using conventional fungal isolation techniques

Management of Allergic Fungal Sinusitis

- Allergic fungal sinusitis (AFS) is a chronic problem with no cure, is not a disease in the true sense, nor an infection.
- AFS is:
  - Type 1 hypersensitivity reaction
    - May begin as locally mediated IgE response in which IgE may not be detected in the peripheral blood
  - Eosinophil mediated inflammation
    - Eosinophil cationic protein
    - Eosinophilic peroxidase
    - Eosinophilic derived neurotoxin
    - Major basic protein
Possible Strategies for Treating CRS

Treat Etiology
- Antibiotics
- Antifungals
- Surgery

Attenuate Inflammation
- Steroids
- Anti-IgE or IL-5
- Immunotherapy
- Antileukotrienes
- Macrolides
- Who knows what else?

CRS
Rhinosinusitis Adjunctive Treatments

- **Oral Steroids**
  - Extremely beneficial in chronic rhinosinusitis with polyps
  - Role in allergic rhinitis?
  - Longer than 10 days should be tapered
  - “Dose packs”, fall to sub-therapeutic levels after two days

- **Direct risk relationship with long term steroid use**
  - Low dose/short terms: weight gain, insomnia, mania/dysphoria, aseptic necrosis of the hip
  - HPA suppression, ocular hypertension, osteoporosis, **** cataracts
Rhinosinusitis Adjunctive Treatments – Intranasal Steroids

- First generation intranasal steroids
  - Beclomethasone
    - Breakdown product as active metabolite

- Second generation intranasal steroids
  - Budesonide, fluticasone, mometasone
    - Greater in-vitro potency; longer half lives
    - No HPA suppression at standard doses
    - Nearly complete metabolized by liver on first pass
    - Clinically similar efficacy in allergic rhinitis between different agents
Rhinosinusitis Adjunctive Therapies - Decongestants

- Reduces mucosal edema
  - Topical oxymetazoline/neosynephrine
  - Pseudoephedrine
  - Phenylpropanolamine
  - Females 16.5 X increase risk of hemorrhagic stroke with diet medications; 3.13 X increase risk with cold medications*

- Little experimental support but subjectively good

- Never more than 72 hours for inhaled decongestants

Rhinosinusitis Adjunctive Treatments

- **Mucolytics (guaifenesin)**
  - Probable beneficial in both acute and chronic rhinosinusitis

- **Nasal saline irrigation**
  - Hypertonic saline improves mucociliary clearance*
  - Hypertonic saline improves rhinosinusitis quality of life*

Rhinosinusitis Adjunctive Therapies – Nebulized Antibiotics

- Usually not covered by insurance plans
- Have been available for approximately 5 years
- Limited number of studies available
- Most studies are in patients that are post surgical
Rhinosinusitis Adjunctive Therapies – Antifungals

- Experience limited *
  - 2 positive uncontrolled reports using antifungal nasal lavage with amphotericin B on nasal polyposis
  - 1 controlled report no improvement
  - 1 controlled report with mixed results
  - 1 showing significant improvement based on CT and endoscopy*

**Allergic Fungal Sinusitis**

- Few patients will remain clear without active treatment for greater than a year.

- Must control either:
  - The fungus
  - The inflammatory reaction to the fungus
  - The allergic response to the fungus

- Treatment should be directed towards:
  - Reducing inflammation - anti-inflammatory drugs.
  - Reducing Type 1 hypersensitivity - desensitize & antihistamines
  - Reducing the exposure to fungus - environmental fungal reduction in (home, work, recreational).
  - Kill fungus in nose - antifungal oral or irrigation.
Factors That Influence Clinical Outcome

Proper Diagnosis: Bacteria versus virus, allergy, anatomic obstruction, rhinitis medicamentosa, etc.

Likely microbes, resistance patterns, antibiotic PK/PD properties, allergy, adverse effects, convenience, palatability, cost

Antibiotic choice

Clinical Outcome
Surgical Treatment of Chronic Rhinosinusitis
“Sinus Headache”

- Cephalgia without nasal symptoms is rarely due to rhinosinusitis
- From 40% - 80% of patients with symptoms consistent with sinus headaches fulfill the diagnostic criteria for migraine
- Migraine may present with unilateral nasal congestion, rhinorrhea (typically clear) and facial pain

In short, patients complaining of facial congestion, headaches, without nasal symptoms, almost never has acute sinusitis
Rhinosinusitis is first and foremost a medical disease that requires aggressive medical therapy. Appropriate treatments are aimed at presumed etiology. Primary therapy involves antibiotics. Adjunctive therapies offer significant advantages as well.
Theories of Chronic Rhinosinusitis Disease

- Mucousal infectious disease
- Osteitis
- Fungal antigen
  - Superantigen