Where Does Sinusitis Come From?

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Disclosures

- **Consultant**
  - Sinuwave
  - Laurimed
  - Entrigie
  - Nasoform
  - Olympus Gyrus

- **Speaker**
  - Stryker
  - Genentech

- **Stockholder**
  - Entrigie
  - Remedease
  - Nasoform
Objectives

- To define rhinosinusitis
- To discuss several proposed extrinsic mechanisms of the disease
  - Mucosal infection
  - Fungal infection
  - Staph Superantigen
  - Biofilms
  - Bone inflammation
- To review intrinsic mechanical and immunological defects in the disease
We Think We Know Everything...
## Factors Associated in Diagnosis of Rhinosinusitis

**MAJOR**
- Nasal obstruction/blockage
- Hyposmia/anosmia
- Purulence in nasal cavity on examination
- Fever* (in children)
- Facial pain/pressure* (used in conjunction with other factors)

**MINOR**
- Headache
- Fever (all nonacute)
- Halitosis
- Fatigue
- Dental pain
- Cough
- Ear Pain /pressure/fullness

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Lanza, DC, Kennedy, DW, Adult Rhinosinusitis Defined  Otolaryng Head Neck Surg 117; S1-7, 1997

Rhinosinusitis Task Force, AAO/HNS, 1995

**Diagnosis:** 2 Major or 1 Major and 2 Minor
“A Diagnostic Dilemma for Chronic Rhinosinusitis: Definition Accuracy and Validity”

  - 78 patients prospectively evaluated and meeting criteria
  - Only 37/78 with positive CT-No correlation between CT and severity of symptoms
What is Chronic Rhinosinusitis?

• **Old Paradigm**
  » Chronic Rhinosinusitis is a mucosal infectious disease
  » A “plumbing problem”

Swelling

Bacterial Infection

Obstruction

Mucus Stasis
New Paradigm

- Rhinosinusitis is mucosal inflammation

- CRS Defined By
  - 12 or more weeks in duration
  - Physical findings on endoscopy or anterior rhinoscopy
  - CT helpful, but not necessary

  » Otolaryngol HNS, 120(3), Sept 2003

» Where does the inflammation arise from?
Microbiology of Acute Bacterial Rhinosinusitis (Adults)

- **S. pneum** (20-43%)
- **H. influenzae** (22-35%)
- **Strep spp.** (3-9%)
- **Anaerobes** (0-9%)
- **M. catarrhalis** (2-10%)
- **S. aureus** (0-8%)
- **Other** (4%)

Sinus & Allergy Health Partnership Guidelines for Treatment of Acute Bacterial Sinusitis  Otolaryngol Head & Neck Surg  July 2000
Microbiology of Chronic Sinusitis

Prospective evaluation of 174 adults with CRS requiring surgery had cultures of maxillary sinus.

Most common isolates:

- Coag-neg staph 36%
- S aureus 25%
- Strep viridans 8.3%
- Corynebacterium 4.6%
- Anaerobes 1.4%

Biel MA, et al
Ann Otol Rhinol Laryngol
1998;107:942-5
Theory 1: Mucosal Infectious Disease
Microbiology of Chronic Sinusitis- Post-op

Am J Rhinol. 2006 Jan-Feb;20(1):72-6

Single Culture Performed N = 48

- Staph aureus: 18%
- Coag neg. staph: 30%
- Pseudomonas: 11%
- Other: 32%
- None: 9%

> 3 Cultures Performed N = 17

- Staph aureus: 22%
- Coag neg. staph: 15%
- Pseudomonas: 24%
- Other: 9%
- None: 30%
Theory 2: Fungal Involvement in Chronic Rhinosinusitis

- Fungal cultures were positive in 202/210 consecutive CRS patients
- Allergic mucin was found in 97/101 consecutive surgical cases
- Therefore “all CRS is fungal sinusitis”
  - But, 14/14 controls were also fungus positive with the identical fungal organisms seen in the CRS group.
Theory 2: Fungal Involvement in Chronic Rhinosinusitis

- Similar findings reported in Austria
  - Positive fungal cultures in 84/92 patients
  - Controls positive in 21/23
- Nasal mucosa of neonates
  - 5 days-40%; 4 months-94%
- Conventional fungal isolation not as successful
  - 45 random CRS specimens: 56% positive
Effect of Antifungal Treatment on Inflammation in CRS

- Ampho B BID in the nose for 13 weeks and levels of proinflammatory cytokines, chemokines, and growth factors
  - IL-1beta, IL-1RA, IL-2, IL-2R, IL-3, IL-4, IL-5, etc. TNF-alpha, IFN-gamma, RANTES, eotaxin, etc.
  - No effect on any marker of inflammation

Laryngoscope 2009 Feb;119(2):401-8
Theory 3:

Staphylococcus Aureus Superantigen

Staph Super-antigen

- 25% of the population are carriers of staphylococcus aureus
- Enterotoxin and TSS toxin both exhibit super-antigen activity
  - Less specific Cross-linking T cell receptor with the MHCII on APC
  - May cause 20-25% of all T Cells to be activated
    - normal stimulation will result in 1/10,000
  - Has a role in atopic dermatitis, Kawasaki’s disease, TSS, and rheumatoid arthritis
Theory 4: Biofilms

“an assemblage of microbial cells enclosed in a self-produced polymeric matrix that is irreversibly associated (not removed by gentle rinsing) with an inert or living surface”

- Reduced oxygen and nutrient state
- Increased antibiotic resistance
- 99% of all bacteria are believed to exist in biofilms and only 1% in planktonic state
- CDC: 65% of all human bacterial infectious processes involve biofilms
- First noted by Van Leeuwenhoek
- Reemerged in 1970s
Theory 4:

**Biofilms**

- 24/30 (80%) of pts with CRS demonstrated biofilm by SEM.
- 4 controls were normal.
- Bacteria ided using TEM
- Using fluorescent in situ hybridization (FISH), specific bacteria can be ided in the biofilm
  - 14/18 (78%) with biofilms. 2/5 controls were positive
  - H flu, S pneumo, SA all ided. PA not identified
  - Intraop cultures did not correlate with biofilms ided
Theory 4: Biofilms

40 patients retrospectively followed with CRS undergoing FESS

- 50% with biofilms by confocal scanning laser microscopy
- Patients with biofilms had significantly worse
  - Preoperative symptom scores
  - Preoperative radiologic scores
  - Postoperative symptom scores
  - Postop mucosal appearance
- Presence of polyps, eosinophilic mucin, or pus did not result in poor outcomes
- Psaltis et al. AJR 22, 1-6, 2008
Theory 5: Bone Inflammation

Clinical Evidence
- CT scan findings of thickened bone in paranasal sinuses
- particularly in individuals with recalcitrant disease

Quantitative Histomorphometry
- Results: significant increase in bone activity seen in chronic rhinosinusitis
  - 70% of CRS showing moderate to marked activity
  - 70% of controls showed no activity
- Similar to chronic osteomyelitis
Etiology of Chronic Osteomyelitis in Long Bones

- 80% of Osteo is caused by staph aureus
  - Despite effective antibiotics for sa, infections tend to be persistent and recurrent
- One Theory: intracellular staph aureus
  - Other bacteria had long been known to invade “non-professional phagocyte” cells
    - Salmonella, tuberculosis, shigella, and listeria
  - Recently suggested as the etiology of endocarditis by SA invasion of endothelial cells
    - Thromb Hemostasis 2005;94:266-77
  - Also now implicated in prostatitis, cystic fibrosis, Darier’s disease
Yes, But Does This Have any Relation to the Nose?

- ICSA now identified in nasal epithelium, glandular, and myofibroblastic cells in patients with SA cultured from MM
  - Inverted confocal laser scan fluorescence and TEM from biopsies following abx treatment

- Follow-up study 27 pts who underwent surgery with one year follow-up
  - 17/27 (65%) had ICSA
    - 11/17 with ICSA relapsed over the ensuing year
    - 9/17 (>50%) had SA on MM cx
    - 2/12 (16%) without ICSA had SA on MM cx
    - “presence of ICSA in nasal epithelial cells is a significant risk factor for recurrent RS”
      - Plovin-Gaudon, et al. Rhinology 2006;44:249-54
So A Relationship Exists, But…

- ICSA is probably pathogenic, but maybe a protective response by the cells?
- About 30% of cultures in CRS are SA (vs 80% in chronic osteo), what about the rest?
  - About 30% is coag neg staph—could this also go intracellular? Other bugs?
- What about the bone?
What about the Immune System?

- CRS occurs at the interface of the nasal mucosa and the world
  - Is the immune system hypo-, hyper-, or dysfunctional in CRS?
  - Much of the pathology in CRS is collateral damage
Normal Immune Function

• Innate Immunity
  » Inborn resistance that is present before the first pathogen exposure
  » Initiated by membrane-bound and cytoplasmic pattern recognition receptors (PRRs) that recognize
    » pathogen associated molecular patterns (PAMPs) in viruses, bacteria, mycobacteria, yeast, parasites= danger signal
    » cellular damage through detection of debris from necrotic cells= damage signal
**Cytoplasmic PRRs**

- **Toll-like Receptors (TLR)**
  - Transmembrane receptor on many cell types including respiratory epithelial cells
  - Subtypes respond to gram positive bacteria (including staph), fungal PAMPs, viral replication, etc.

- **NOD-like Receptor Family**
  - Recognize bacterial cell wall products including staphylococci

- **Recognition of PAMPs by Cytoplasmic PRRs results in secretion of cytokines and stimulation of APCs and chemokines that attract cellular components of the immune response**
Acquired Immune System

• Dendritic cells (APCs) become activated after stimulation by PRRs, migrate to LNs and present antigen to Th cells
  » IL6 is the key cytokine mediating the transition from innate to acquired response
  » **TH1 response**—IL12 and IFN gamma facilitate defense against intracellular pathogens (ie, bacteria)
  » **TH2 response**—IL4, IL5, and IL13 facilitate defense against parasites and are assoc with allergy and asthma
But wait, there’s more!!

- TH 17 and T reg are 2 other Th subsets
  - TH 17 is more akin to TH 2 with IL 17 in CRSwNP
- Modulation
  - TH 1 and 2 inhibit one another
  - TGF beta 1 promotes T reg, except in the presence of IL6
  - T reg response is inactivated in situ by strong PRR stimulation, mostly TLR2
Summary

- Sinusitis is first and foremost a medical disease and requires aggressive medical therapy.
- Appropriate treatments must be aimed at presumed etiologies.
- Multiple etiologies probably exist for rhinosinusitis.
  - Extrinsic Contributers
  - Intrinsic Immune Barrier Problems
    - Innate
    - Acquired
“The Lord God ... breathed into his nostrils the breath of life, and the man became a living being.”

Genesis 2:7