Chronic Rhinosinusitis

Daniel Hamilos, MD
Massachusetts General Hospital
Boston, Massachusetts
Disclosures for:
Daniel Hamilos, MD

For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

Honoraria received from:  None
Consulted for:  None
Held Common Stock in:  None
Research, clinical trial, or drug study funds received from:  Merck

I will be discussing products that are investigational or not labeled for use under discussion.
Case presentation

- 58 yo Caucasian male
- 2 yr hx of recurrent sinus infections treated with multiple Ab
- Sinus CT abnormal with multiple areas of sinus opacification
- Adult-onset asthma that flares with sinus disease
- Sinus surgery performed, revealing polyps, allergic mucin and infection with Staphylococcus aureus (no fungus found)
- Postoperatively, failure to resolve mucosal inflammation
- Persistent evidence of infection/colonization with Staphylococcus aureus or Pseudomonas aeruginosa
- Positive allergy skin tests for multiple fungi
- Failure to resolve despite aggressive topical steroid rinses
Chronic rhinosinusitis (CRS)

- CRS without NP
  - With other inflammatory features
    - Vaso-motor rhinitis
    - Non-allergic rhinitis
    - GERD
    - Sarcoidosis
    - Non-allergic rhinitis

- CRS with NP
  - With eosinophilic inflammatory features
    - Without fungal hyphae
      - ASA tolerant
      - ASA sensitive
    - Eosinophilic mucin with fungal hyphae (and positive fungal skin tests) “classic AFRS”
      - ASA tolerant
      - ASA sensitive

Allergic rhinitis

- Bacterial Infection
  - Anatomic abnormalities, humoral immune deficiency, abnormal mucociliary function

What underlies CRS?  
**CRS Epidemiology – role of allergies**

- Increased prevalence of IgE-mediated in CRS (with and without NP)
  - 60% compared to 30-40% in the general population.

- Patients are typically sensitized to perennial allergens.

- Histopathologic studies of ethmoidal and nasal polyp tissue show that allergic CRS patients have chronic allergic inflammation
  - T cell infiltration and local production of Th2 cytokines, IL-4, IL-5, and IL-13.

- However, the intensity of eosinophilic inflammation in CRSsNP and CRSwNP is independent of systemic allergy ("local allergy").
CRS Epidemiology – role of immunodeficiency

- In pediatric CRS, 34 of 61 children with refractory CRS had abnormal immune studies, with depressed IgG3 levels and poor response to pneumococcal antigen being the most common.

- In adult CRS, 22.8% of refractory CRS cases had a low IgG2, IgG3 or combined defect of major and/or minor IgG subclasses.

- In adult CRS, the prevalence of any type of low immunoglobulin or poor response to vaccination in 12.7% of CRSsNP patients and only 2.2% of patients with CRSwNP.

- Deficiency in innate immunity?
What is the role of inflammation, and what are the components of chronic inflammation?

Chronic rhinosinusitis (CRS): “an inflammatory disorder of the nose and paranasal sinuses”.

CRS is unlike ABRS and should be viewed and treated differently.

... look for things that can cause inflammation, i.e.

- Chronic allergic inflammation
- Chronic eosinophilic inflammation
- Dysregulated tissue factors (e.g. TSLP?)
- Chronic bacterial infection
- Bacterial colonization
- Fungal colonization
Normal Transportation Pathways of Mucus in the Maxillary Sinus

The term “OMU” has been used to refer to the maxillary sinus ostium, anterior and middle ethmoidal air cell ostia, nasofrontal duct (frontal recess), infundibulum, or the middle meatal complex.
Complex interaction between innate and adaptive responses in CRS

- **Adaptive immune function**
  - $T_{H1}$
    - IL-12, IFN-γ
  - $T_{H2}$
    - IL-4, IL-13
  - $T_{H17}$
    - IL-17, IL-22
  - TReg
    - TGF-β, IL-10
  - B
    - Antibody production

- **Innate immune function**
  - Dendritic Cell
    - TSLP
    - IL-33
  - Mast Cell
  - IL-25

- **Pathogens**
  - Allergen
  - Viral infection
  - Bacterial Infection/colonization
  - Fungal colonization

- **Cytokines and Growth Factors**
  - BAFF, APRIL
  - IL-10
  - IL-12, IFN-γ
  - IL-13
  - IL-17
  - IL-22
What insights can we glean from the current CRS classification?

Chronic rhinosinusitis (CRS)

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Bacterial Infection

Anatomic abnormalities, humoral immune deficiency, abnormal mucociliary function

Allergic rhinitis

Rhinosinusitis diagnostic criteria

**Recurrent acute RS**

A. Recurrent acute rhinosinusitis $>3x/\text{year}$
B. Requires $\geq 2$ of the following symptoms:
   - Ant or post mucopurulent drainage
   - Nasal congestion
   - Facial pain/pressure
   - Decreased sense of smell
C. Normal between episodes

**CRSwithNP**

A. Symptoms present for $\geq 12$ weeks
B. Requires $\geq 2$ of the CRS symptoms
C. Objective documentation
   - Rhinoscopic exam
   - X-ray (sinus CT preferred)
   - CRSwithNP: requires bilateral nasal polyps in middle meatus.

**CRSwithoutNP**

A. Symptoms present for $\geq 12$ weeks
B. Requires $\geq 2$ of the following symptoms:
   - Ant or post mucopurulent drainage
   - Nasal congestion
   - Facial pain/pressure
   - Decreased sense of smell
C. Objective documentation
   - Rhinoscopic exam
   - X-ray (sinus CT preferred)

**AFRS**

A. Symptoms present for $\geq 12$ weeks
B. Requires $\geq 2$ of the CRS symptoms
C. Objective documentation
   - Rhinoscopic exam
   - X-ray (sinus CT preferred)
D. AFRS criteria
   - Positive fungal stain or culture of allergic mucin
   - IgE-mediated fungal allergy
The spectrum of adult CRS cases in a referral institution (MGH)

At MGH (N=100 patients with CRS):

- 64% had prior surgery
- 40% had history of NP
- Approx. 50% had polyps or polypoid mucosa
- Approx. 50% have perennial allergies
- Approx. 12% had either confirmed or suspected AFRS (suspected AFRS have “allergic mucin” with negative fungal stains and culture)

Patterns of illness in CRSsNP vs CRScNP vs AFRS

**CRS without NP**
most common form (60-65% of cases)
structural abnormalities, sinus ostial obstruction, defects in mucociliary clearance or immunodeficiency are more likely in this subset.

**CRS with NP**
Second most common form (30% of cases)
Diffuse sinus involvement and strong adaptive response (eosinophilic) to colonizing *S. aureus* are more likely in this subset.
Asthma more likely than in CRSsNP.
ASA-intolerance more likely than in CRSsNP.

**Allergic fungal rhinosinusitis (AFRS)**
Least common form (5-7%)
Can be diffuse or localized, intensely strong adaptive response (eosinophilic and IgE) to colonizing fungi are most likely in this subset.
Otherwise similar to CRSwNP.

Most characteristic symptoms:

- **Facial pain/pressure/HA**
- **Anosmia/hyposmia**

Histopathology:
Chronic inflammation with mononuclear infiltrate and increased neutrophils
Glandular hyperplasia

Symptoms:
Facial pain/pressure/fullness
Anterior or posterior nasal drainage

Sinus CT imaging:
Sinus ostial occlusion
Sinus mucosal thickening
Sinus opacification
 +/- air-fluid levels

Nasal endoscopy:
Purulence in middle meatus
Maxillary erythema, edema with overlying mucus

Histopathology:
Chronic inflammation with mononuclear infiltrate and increased neutrophils
Glandular hyperplasia
CRSwithoutNP
**Bacterial biofilm properties**

- Unique extracellular bacterial microenvironment.
- Commonly associated with growth of bacteria on an inert surface.
- Involves formation of clusters of microbial organisms held together by an extracellular glycocalyx with interspersed water channels.

Courtesy of Dr. David Davies, Binghamton University, Binghamton, NY.  
http://www.erc.montana.edu/biofilmbook/MODULE_01/Mod01_IntroPage.htm.
Bacterial biofilm in sinus mucosa in CRS

- Multiple studies have demonstrated bacterial biofilm in 45 - 80% of adult CRS cases.
- There is a low rate of biofilm in healthy control subjects.

Healthy control with no biofilm

Bacterial biofilm in CRS patient

Bacterial biofilm in CRS patient

Epithelial innate immunity involves Toll-like receptors

Bacterial exposure

- Sinonasal epithelial cells express TLRs 1 - 10.
- TLR2, TLR3, TLR4 and TLR9 pathways are functional.

Proinflammatory response
- IL-8, GRO-α, RANTES, etc.
- β-defensins
- cathelicidins
- PLUNC proteins

http://encyclopedia.vbxml.net/CD14
Substances involved in epithelial innate immunity

1. Antimicrobial peptides
   - α-defensins
   - β-defensins (inducible)
   - cathelicidins (inducible)
   - PLUNC proteins

2. iNOS

3. Innate factors with unknown function

4. Proinflammatory cytokines and chemokines
   - TNF-α, IL-6
   - CXC chemokines (IL-8, others)
   - CC chemokines (RANTES, eotaxins, etc.)
Can we identify innate immune defects in CRS

- Schleimer RP et al studies of CRSsNP versus CRSwNP.
- Decreased epithelial expression of mRNA for S100A7 (psoriasin) and S100A8/A9 (calprotectin) in CRSwNP.
  - Tieu DD et al. JACI 2010; 125: 867

- Desrosiers M, et al “refractory CRS” following surgery and medical Rx.
- GWAS studies reveal polymorphisms in IL-22Rα1 and SERPINA1

- Ramanathan M, Lane AP et al “recalcitrant CRS” based on recurrence of nasal polyps following polyp surgery.
- Reduced TLR9 expression and reduced IL-22R expression

- Reduced levels of lactoferrin in biofilm-associated CRS.
- 15-fold reduction in lactoferrin mRNA and 3-fold reduction in tissue lactoferrin protein in biofilm-associated CRS.
Connecting innate immune defects to refractory CRS

- Bitter taste receptors are expressed on ciliated sinus epithelial cells.

- G-protein coupled receptors - signal by inducing a transient intracellular calcium flux and stimulating ciliary beat frequency.

- Family of receptors with several molecule variants with differential capacity to signal.

- Non-taster variant has reduced signaling.

- Do these receptors have a function in sinus epithelium?

Connecting innate immune defects to refractory CRS

- T2R38 bitter taste receptor is activated by quorum-sensing molecule from *Pseudomonas aeruginosa* (associated with biofilm formation).

- Activation induces production of nitric oxide (NO) and increased ciliary beat frequency (CBF) in sinus epithelial cells.

- A common polymorphism (TAS2R38 variant) is associated with reduced signaling, reduced NO production and reduced CBF.

- TAS2R38 variant linked to reduced ability of sinus epithelial cells to kill *P. aeruginosa*.

- TAS2R38 genotype correlated with presence of sinonasal gram-negative bacterial infection in CRS patients.

<table>
<thead>
<tr>
<th>Functional and nonfunctional allele frequency</th>
<th>TAS2R38&lt;sup&gt;A&lt;/sup&gt;</th>
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<tr>
<td>AVI/AVI</td>
<td>13</td>
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<tr>
<td>AVI/PAV</td>
<td>11</td>
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<tr>
<td>PAV/PAV</td>
<td>11</td>
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</table>

<table>
<thead>
<tr>
<th>No growth</th>
<th>AVI/AVI</th>
<th>AVI/PAV</th>
<th>PAV/PAV</th>
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</thead>
<tbody>
<tr>
<td>Gram-negative <em>P. aeruginosa</em></td>
<td>7</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Total (no growth + gram-negative)</td>
<td>20</td>
<td>25</td>
<td>11</td>
</tr>
</tbody>
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Chronic rhinosinusitis

- Chronically inflamed tissue

- Clinical/pathologic subsets are identifiable

- Few pathophysiologic correlates thus far

- More precise phenotyping of CRS is likely to evolve

- Complex interaction between local infection and inflammatory processes

\[
\text{Innate immunity} \quad - \quad \text{(Th2)}
\]

- Infection

- Inflammation

+
Paradigm shift in CRS classification scheme

- Eosinophilic mucin
  - Abnl systemic immunity
    + ASA sensitive
    - ASA sensitive
  - Abnl innate immunity
    - biofilm
    + biofilm
    + bacterial infection
    - bacterial infection
    + fungi
    - fungi
    - bacterial infection
  - NI innate immunity
    + biofilm
    + bacterial infection
    - bacterial infection
    - fungi

CRSsNP
Histopathology:
Edematous tissue with chronic mononuclear infiltrate and increased numbers of eosinophils
Increase in IL-5 producing T lymphocytes (strong local Th2-type response)

Symptoms:
Nasal congestion
Facial pressure/fullness
Postnasal drainage
Hyposmia or anosmia

Sinus CT imaging:
Bilateral disease
Sinus opacification or polypoid mucosal thickening
Nasal polyps

Nasal endoscopy:
Polypoid mucosal thickening
Nasal polyps

CRSwithNP
The histopathology of CRSwithNP

- A. Nasal polyps.
- B. Eosinophil infiltration.
- C. Increased IL-5+ Th2 cells.
- D. Production of RANTES and eotaxin by epithelial and inflammatory cells.
- E. Endothelial expression of VCAM-1.
- F. Expression of TNF-α.
Pathogenesis of CRS: the “fungal hypothesis”

Emerging evidence demonstrates an important role for fungal Th2 hypersensitivity in CRS pathogenesis.

- Fungal hyphae in mucus in >90% of cases
- Eosinophils in mucus attack hyphae and degranulate


- Clusters of eosinophils in mucus
- MBP release within the clusters
Fungal Th2 hypersensitivity in CRS


Seen in CRS patients but not in normal controls.

Fungal culture extract

IL-5, IL-13
IFN-γ

Induce epithelial eotaxin
Eosinophil activation

Similar to the cytokine profile in NP and T lymphocytes isolated from NP.

Alternaria

0
10
20
30
40
50
60
70

IL-13 pg/ml

Contrasting view to fungal hypothesis

- Failure to reproduce findings of Ponikau et al (1).
- Staphylococcal enterotoxin SEB is a much more potent stimulus for IL-5, IL-13 and RANTES production from dispersed NP cells (2).

*Staphylococcus aureus* colonization as an immune stimulant in CRSwithNP but not in nonpolypoid CRS

- **S aureus** colonization rates:
  - Controls: 33.3%
  - Nonpolypoid CRS: 27.3%
  - CRScNP: 66.7%
  - CRScNP + asthma + ASA: 87.5%

- In patients with NP, there is local IgE production against superantigens (SA) from *Staphylococcus aureus*

- Local IgE production even occurs in “nonallergic” patients.

Induction, distribution and modulation of upper airway allergic inflammation in mice.

Nasal polyp pathogenesis

- Nasal polyp formation can be induced by allergic sensitization/exposure followed by exposure to SEB.
- Hypoxia-inducible factor 1 (HIF-1α) and HIF-2α are upregulated in mouse model of nasal polyposis.
- HIF-1α and HIF-2α mediate epithelial-mesenchymal transition (EMT).

Hypoxia-inducible factor 1 (HIF-1α) and HIF-2α are upregulated in mouse model of nasal polyposis.

HIF-1α and HIF-2α mediate epithelial-mesenchymal transition (EMT).

Nasal polyp pathogenesis involves epithelial-mesenchymal transition (EMT).

Antibiotics for nasal polyposis?

- A RDBPC trial was conducted comparing doxycycline (200 mg on day 1 then 100 mg daily for 20 days) versus placebo.

- Doxycycline caused a small but statistically significant reduction in NP size beginning at week 2 and persisting for 12 weeks.

- A reduction in nasal secretion eosinophil cationic protein (ECP) was also found after 20 days treatment.

- No significant improvement in nasal peak inspiratory flow rate.

- The effects of longer term treatment with doxycycline on NP size and clinical outcomes remain to be studied.

Histopathology:
Edematous tissue with chronic mononuclear infiltrate and increased numbers of eosinophils; clusters of eosinophils in mucus
Fungal hyphae in mucus

Symptoms:
Nasal congestion
Facial pressure/fullness
Postnasal drainage
Hyposmia or anosmia

Sinus CT imaging:
Sinus opacification
Hyperdense material in opacified sinus
Bony erosion (20%) 
Nasal polyps

Nasal endoscopy:
Polypoid mucosal thickening
Nasal polyps
Allergic mucin

Hematoxylin/eosin stain
Immunofluorescence stain of fungal hyphae
Fungal hyphae in mucus

Histopathology:
Edematous tissue with chronic mononuclear infiltrate and increased numbers of eosinophils; clusters of eosinophils in mucus

Allergic fungal rhinosinusitis
Classic allergic fungal rhinosinusitis

Accounts for 7% of CRS cases overall.

Wide geographic differences in prevalence.

Usually caused by dematiaceous fungi, s/a
- Bipolaris
- Alternaria
- Aspergillus

This is not the fungal hypothesis!!

I. Diagnosis of “Classic” AFRS

A. Pattern of symptoms
- Symptoms present for ≥12 weeks

B. Symptoms for diagnosis
- Requires ≥1 of the following symptoms:
  - Anterior and/or posterior mucopurulent drainage
  - Nasal congestion
  - Decreased sense of smell
  - Facial pain/pressure

C. Objective documentation by all:
  - Endoscopy to required to document presence of inflammation such as discolored mucus or edema of middle meatus or ethmoid area, or nasal polyps.
  - Imaging by CT or MRI
  - Presence of allergic mucin (containing fungal hyphae with degranulating eosinophils)
  - Evidence of fungal-specific IgE
Aspirin-intolerance in NP patients: metabolic abnormalities present (~ 15% of NP patients)

- Increased baseline production of cysteiny1-LTs (C4,D4,E4) in bronchoalveolar lavage (BAL).
- Increased baseline urinary LTE4.
- Increase in LTC4 synthase+ inflammatory cells in airway biopsies.
- Increase in nasal, BAL and urinary LT production in response to ASA challenge.
- Underproduction of PGE2 in nasal polyp epithelial cells.
- Increased baseline expression of Cys-LT1 receptors on inflammatory cells in NP.

Clinical classification of CRS

Chronic rhinosinusitis (CRS)

Anatomic abnormalities, humoral immune deficiency, abnormal mucociliary function

Bacterial Infection

CRS without NP

With other inflammatory features

Vaso-motor rhinitis

Non-allergic rhinitis

GERD

Sarcoidosis

Non-allergic rhinitis

With eosinophilic inflammatory features

CRS with NP

With eosinophilic inflammatory features

With fungal hyphae

Without fungal hyphae

Eosinophilic mucin with fungal hyphae (and positive fungal skin tests) “classic AFRS”

ASA sensitive

ASA tolerant

ASA sensitive

ASA tolerant

Allergic rhinitis

With other inflammatory features

Clinical classification of CRS

Evaluating the CRS patient

CRSwithoutNP
CRSwithNP
AFRS
Recurrent acute RS

Clinical Classification

Reevaluate
Initiate treatment
Evaluate for an infectious cause
Review Sinus CT scan
Evaluate contributive factors

topical steroids
intranasal saline
antibiotics
topical antifungals
adjunctive therapies
immunotherapy

perennial allergy
indoor allergen exposure
cigarette smoke exposure
asthma
aspirin sensitivity
immune deficiency
Evaluating the sinus CT scan: significance of sinus opacification

CRSwithoutNP - should be assumed to represent an infectious process until proven otherwise.

CRSwithNP - in the absence of infection and should not always be assumed to be an infection. Could represent:
  - inflammatory mucosal thickening
  - polypoid mucosal thickening
  - mucus accumulation
  - mucus inspissation

AFRS may simply represent polypoid mucosal disease but may also represent mucus impaction with allergic mucin laden with fungal hyphae.
Case #1: CRS without NP

Case #2: What is the problem?
Case #2: CRSwithoutNP

To quote Stammberger*: If sinusitis does not heal or recurs constantly, a focus of reinfection usually persists in one of the narrow clefts of the anterior ethmoids...from these areas infection may spread locally to involve the prechambers and the larger sinuses.

(New concept) This persistence of infection may be due to local biofilm formation.

Case #3: CRSwithoutNP

Case # TH
31 yo African-American female with no prior history of sinus surgery, nasal polyposis or asthma.

Symptoms: nasal congestion, frequent nose blowing with clear to white mucus, post-nasal drainage and vague facial fullness.

Exam: enlarged nasal turbinates with white mucoid drainage. Otherwise negative.

Allergy skin tests all negative.

Nasal endoscopy
(= fiberoptic rhinolaryngoscopy)

- Assess sphenoid recess
- Assess middle meatus
- Postoperatively, assess sinus cavities
- Obtain sinus cultures
- (Remove mucus)
Antibiotics to remove chronic bacterial infection or colonization. Controlled trials are lacking.

Use a broad-spectrum antibiotic that is beta-lactamase stable, effective against penicillin-resistant S. pneumoniae, and possesses anti-anaerobic coverage. E.g.

- combination of a penicillin (e.g. amoxicillin) + clavulanic acid or clindamycin
- combination of a macrolide or fluoroquinolone + metronidazole

Treat for 21-28 days combined with a short course of systemic Prednisone ("Intensive Medical Treatment").
Excellent response to:

Prednisone
   20 mg BID x 5 days
   20 mg daily x 5 days

Augmentin
   875 mg bid x 4 weeks

This is “intensive medical treatment”.

Long-term macrolide Rx

- Recommended in EP3OS document as level Ib evidence, but based on only a couple studies.

  - RCT medical versus surgical treatment of CRS
  - 90 patients (CRSsNP or CRSwNP) were randomly assigned to medical versus surgical treatment.
  - Medical treatment: erythromycin (500 mg BID for 2 weeks followed by 250 mg BID for 10 weeks), alkaline nasal irrigation, and intranasal steroids for 12 weeks.
  - Surgically treated patients: 2 week course of erythromycin 500 mg BID, dexarhinospray and alkaline nasal douches followed by a 3 month course of fluticasone nasal spray plus alkaline nasal douche.
  - Patients in both the medical and surgical groups significantly improved, and no significant differences in subjective and objective parameters of CRS were found between groups.
Long-term macrolide Rx

- Roxithromycin 150 mg daily vs placebo.
- Patients on roxithromycin showed significant change from baseline in SNOT-20 at 12 weeks not seen in placebo.

- 60 patients with CRSsNP or CRSwNP were randomized to receive azithromycin versus placebo 500 mg daily x 3 days, then 500 mg weekly for 11 weeks
- No significant differences between groups at the end of treatment.
CRS with Nasal Polyposis

- A diffuse bilateral mucosal disease.

- Postoperative appearance with recurrent polypoid disease in anterior ethmoid and maxillary sinuses.
OBJECTIVE: To establish the efficacy of a short course of oral prednisolone in treatment of sinonasal polyposis.

METHODS: DBPCT of treatment with 50 mg of prednisolone daily for 14 days or placebo (20 subjects per group).

RESULTS: Only the prednisolone-treated group showed significant improvement in nasal symptoms (P<.001) and greater improvement in Rhinosinusitis Outcome Measure score (P<.001). There was a reduction in polyp size by nasal endoscopy (P<.001) and MRI (P<.001) in the prednisolone-treated group.

CONCLUSION: A short course of systemic corticosteroids improves the symptoms and pathology of sinonasal polyposis.

CRS: antifungal treatment to remove fungal colonization

- Amphotericin B sinus irrigation:
  - 12 wks treatment caused 9% reduction in inflammatory mucosal thickening vs. 2% in control (Ponikau J et al. JACI 2005;115:125-31.)
  - 12 wks treatment 100 ug/ml bid was ineffective (Ebbens FA, et al. JACI. 2006;118:1149-56.)

- Amphotericin B nasal spray:
  - 8 wks treatment failed to improve sinus CT score
  - (Weschta M, et al. JACI 2004;113:1122-8.)

- Systemic terbinafine:
  - oral 625 mg daily for 8 wks failed to improve sinus CT
  - (Kennedy DW et al Laryngoscope. 2005; 115:1793-9.)
Topical steroids

- Numerous studies have shown that topical intranasal steroids are effective at reducing nasal polyp size or reducing the recurrence of nasal polyps following sinus surgery.

- A few studies of topical steroid irrigations or drops show a superior effect to topical intranasal steroid sprays.
Our experience with topical steroid nasal instillation

Budesonide topical Instillation* (.5 mg + 1 tsp saline per nostril daily):

- Use a syringe to instill the mix into your right nostril.
- Pinch off the nostril and go into head down forward (HDF) position for 1-2 minutes, then in right lateral supine position (LSP) for 1-2 minutes, then in supine position (SP) for 1-2 minutes, then sit up and expel the solution from the nose.
- Then repeat the entire procedure in the left nostril.

Budesonide is not FDA-indicated for treatment of CRS or NP.
Postoperative patient with NP prior to initiation of topical steroid irrigations
Same patient one month after initiation of topical steroid irrigations
Allergic fungal rhinosinusitis (AFRS)
Treatment

- Surgical drainage of allergic mucin
- Prednisone 0.5 mg/kg daily for 2 weeks, then QOD with gradual tapering over several weeks
- Environmental control measures
- Fungal immunotherapy should be considered
- Systemic antifungal therapy is unproven.
- Topical antifungal therapy should be considered (Amphotericin B or itraconazole). Irrigation technique is critical.
- Intranasal corticosteroids are recommended but unproven.
AFRS: antifungal treatment studies

- 12-year retrospective chart review of 139 patients meeting the AFS criteria of atopy, characteristic radiographic findings, eosinophilic mucin, nasal polyps, and a positive fungal culture or stain.

- RESULTS: Although 69 patients (50.3%) experienced recurrence, reoperation was required in only 17 (20.5%) of 83 patients initially managed by our protocol. No serious adverse effects attributed to itraconazole.

- CONCLUSION: The use of itraconazole, short-burst low-dose oral corticosteroids, topical corticosteroids, and endoscopic surgery is a safe and clinically effective regimen in the management of AFS. Medical management with itraconazole may avoid revision surgery.

Treatment Protocol as of 2001

FESS for drainage and fungus removal

LFTs baseline, then every 4–6 weeks

**High-dose oral itraconazole** P.O.D., 1 or 2 or if recurrence
- 400 mg/day for 1 month,
- 300 mg/day for 1 month,
- 200 mg/day for 1 month or until clear by endoscopy.
  If no progress, current level held for an extra 2–4 weeks

**Low-dose oral prednisone burst** P.O.D., 1 or 2 or if recurrence with polyposis
- 30 mg/day for 3 days,
- 20 mg/day for 3 days,
- 10 mg/day for 7 days; repeated if flare

Normal dosage topical nasal steroid P.O.D., 14

Recommended maintenance dose (2 puffs each nostril every day) until endoscopically clear

Allergy referral Immunotherapy as indicated

Aspirin desensitization for AERD

- Experience with > 400 ASA desensitizations (Scripps Clinic).
- Risk factors for severe reactions during desensitization (1):
  - Lack of leukotriene modifier use
  - Baseline FEV1 < 80% predicted
  - Previous asthma-related emergency department visits
- Target dose of desensitization = 650 mg ASA.
- Maintenance dose ASA (2):
  - Both 650 mg BID and 325 mg BID maintenance dosages were efficacious, and side effects are similar in both groups
  - Some patients initially taking 325 mg BID require an increase to 650 mg BID for optimal symptom control.

Functional endoscopic sinus surgery
What is Functional Endoscopic Sinus Surgery (FESS)?

FESS is based on the hypothesis that the ostiomeatal unit is the key area in the pathogenesis of chronic sinus diseases. Minor pathologic changes in the nasal mucosa in the OMU may interfere with mucociliary clearance and ventilation of the maxillary, ethmoidal, and frontal sinuses. Ultrastructural changes of respiratory mucosa can result from acute and chronic infections.
Does Allergic Status Have an Impact on Postoperative Outcomes Following Sinus Surgery?

- Most studies have shown no relationship between allergic status and outcomes following sinus surgery.
  - *Systemic allergic status does not reflect the local Th2 inflammatory process.*

- A relationship has been found between the presence of nasal polyps and poorer outcomes following sinus surgery.

Local production of IL-5, GM-CSF and IL-3 (with increase in eosinophil survival)

NP contain increased numbers of IL-5 producing T lymphocytes.

- IL-5 producing cells in NP:
  - 68% T cells
  - 18% eosinophils
  - 14% mast cells

- IL-5 is the principal survival-promoting cytokine in NP.
- IL-5 promotes eosinophil entry into tissues.
- IL-5 facilitates the action of eotaxin.

Anti-IL-5 treatment for nasal polyposis

- RDBPCT of mepolizumab as a treatment for NP in subjects deemed “refractory” to corticosteroid therapy (defined as “must have had failure of standard care for CRSwNP”).
- Patients received: mepolizumab (N = 20), 2 IV injections 28 days apart of 750 mg of mepolizumab, or placebo (N=10) over a 8 weeks.

**Results:**

- Mepolizumab treatment was associated with a significant reduction in NP size lasting at least 1 month after dosing in 12 of the 20 patients.
- No relationship between mepolizumab response and nasal IL-5 levels.

Omalizumab as a treatment for nasal polyps

- RDBPCT of omaluzumab as a treatment for patients with NP and comorbid asthma.
- Allergic and nonallergic patients were included.
- Subjects received omalizumab (n = 16) or placebo (n = 8) for 16 weeks.

Results:
- Omalizumab treatment was associated with a significant decrease in total nasal endoscopic NP and sinus CT scores after 16 weeks compared to placebo.
- Benefit was seen in both allergic and nonallergic patients.