Treatment modalities in Chronic Rhinosinusitis

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

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

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

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

**Underlying defects:**
Innate immunity?
Mucociliary clearance?
**Histopathology:**
Edematous tissue with chronic mononuclear infiltrate and increased numbers of eosinophils
Increase in IL-5 producing T lymphocytes (local Th2 response)
Maladaptive Th2 response to microbes

**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

**CRS with NP**
Innate immunity and its relevance to microbial colonization and biofilm

Chemokines (IL-8, CXCL-10, GRO-α, RANTES) defensins (hBD-2) cathelicidins PLUNC proteins

Decrease in antimicrobial proteins in mucus (lactofeerin)

Bacterial exposure

Fungal colonization

Bitter taste receptor

Activation of NFκB

SEM CSLM

Toll-like receptors

Proinflammatory response

Interferon Pathway
Treatment options for CRSsNP and CRSwNP

- **Antibiotics**
  - Systemic antibiotics (oral and intravenous)
  - Long-term macrolide antibiotics
  - Topical antibiotics
- **Glucocorticoids**
  - Systemic glucocorticoids
  - Steroid nasal sprays
  - Steroid sinus irrigations
- **Aspirin desensitization** (for ASA-intolerant CRSwNP)
- **Antifungal drugs**
  - Systemic
  - Topical
- **Biologic therapy** (for CRSwNP)
  - Anti-cytokine therapy
  - Anti-IgE (omalizumab)
Long-term macrolide Rx for CRSsNP

- Recommended in EP3OS 2012 document as level Ib evidence.

  - Roxithromycin 150 mg daily vs placebo.
  - Patients on roxithromycin showed significant change from baseline in SNOT-20 at 12 weeks not seen in placebo.
  - Patients with low or normal IgE had better response rate.
Poor prognostic features for CRS response with low-dose macrolide therapy in CRSsNP
(Low-dose = ½ of normal therapeutic dose)

- Atopic predisposition
- High serum IgE (> 200-250 kU/ml)
- Response to effective distribution of topical steroid therapy
- Watery discharge, itch- and sneeze-dominated symptomatology
- Presence of asthma, dermatitis or conjunctivitis
- Ciliary disorders
- Allergic fungal rhinosinusitis
- No previous culture oriented antibiotic therapy
- Suspected eosinophilic inflammation
- High sinus CT score

Harvey RJ et al. Immunology Allergy Clinic N America 29: 689, 2009.
EPOS 2012
Topical antibiotics for CRSsNP

- Most studies of postsurgical patients and culture-directed therapy.

- Nebulized antibiotic for 3 - 6 weeks in prospective observational studies (Scheinberg and Otsuji 2002; Vaughan and Carvalho 2002).

- Excellent to good improvement was reported in 82% of cases. Endoscopic improvement and increase in infection-free interval after treatment (Vaughan and Carvalho 2002).

- Examples:
  - Mupirocin irrigations for patients with refractory CRS with culture-proved S aureus infection (Uren, Psaltis et al. 2008).
  - Topical gentamicin or tobramycin 80 mg/L (Elliott and Stringer 2006).

- Topical antibiotics can be administered with or without a nebulizer.
Systemic antibiotics plus oral steroids is beneficial.
(More benefit has been reported in CRSsNP than in CRSwNP.)

- Retrospective review of 40 pts treated with Ab for 4 wks plus prednisone 20 mg BID 8-10 days.

- All patients received adjunctive treatments, including saline irrigations and intranasal steroids.

- 36 of 40 patients improved symptomatically, radiographically, or both.

- Patients with CRSwNP or a history of sinus surgery were more likely to experience relapse within 8 weeks.
Systemic antibiotics plus oral steroids is beneficial. 
(More benefit has been reported in CRSsNP than in CRSwNP.)


- Children received amox/clav plus deflazacort (1 mg/kg for 2 days, 0.5 mg/kg for 4 days, and 0.25 mg/kg for 4 days) or matching placebo.

- The amox/clav + MP treatment arm was superior in terms of reducing radiographic extent of disease and improving symptoms.

- (No deflazacort alone treatment arm.)
Intranasal steroids for CRSsNP

- **Summary statement:** Intranasal steroids (sprays and aerosols) have been shown to be beneficial for treatment of CRSsNP in some but not all studies. (Evidence level Ia, Ib; Grade A)

- There have been very limited trials of steroid irrigations in CRSsNP.
**CRSwNP: priorities for treatment**

- Reduce size of nasal polyps
- Reduce recurrence of nasal polyps
- Suppress underlying adaptive Th2 response
- Reduce bacterial or fungal colonization (not yet proven effective)
**Systemic steroids for CRSwNP**
(“medical polypectomy”)

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

- **RESULTS:**
  
  Prednisolone Rx associated with:
  
  - significant improvement in nasal symptoms (P<.001)
  - greater improvement in Rhinosinusitis Outcome Measure score (P<.001)
  - reduction in polyp size by endoscopy (P<.001) and MRI (P<.001).

Evidence for fungal Th2 hypersensitivity in CRS: the “fungal hypothesis”

- 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
**CRS: antifungal treatment to remove fungal colonization**

- Neither topical antifungal treatment (sprays and irrigations) nor systemic terbinafine have been demonstrated to provide a benefit for treatment of CRS (Evidence level Ia, Ib)

- Amphotericin B sinus irrigation:
  - 12 wks treatment caused 9% improvement 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.)

- Accentia trial failed to show benefit in CRS (unpublished).

- Systemic terbinafine:
  - oral 625 mg daily for 8 wks failed to improve sinus CT (Kennedy DW et al Laryngoscope. 2005; 115:1793-9.)
Relevance of *S aureus* colonization in CRSwNP

- Increased colonization rate in CRSwNP:
  - Controls: 33.3%
  - Nonpolypoid CRS: 27.3%
  - CRScNP: 66.7%
  - CRScNP + asthma + ASA: 87.5% (Mechanism is unclear.)

- Local IgE production against *S aureus* superantigens, even in “nonallergic” patients.

- Dispersed NP T lymphocytes produce robust IL-5 and IL-13 in response to *S aureus* enterotoxin B (SEB).

- Therefore, *S aureus* is a major driver of the local Th2 inflammation in CRSwNP.

Is eradication of *S aureus* therapeutic in CRSwNP?

- Study: RDBPC comparing doxycycline (200 mg on day 1 then 100 mg daily for 20 days) versus placebo.

- Results:
  - Doxycycline caused a small but statistically significant reduction in NP size beginning at week 2 and persisting for 12 weeks.
  - Nasal eosinophil cationic protein (ECP) was decreased after 20 days treatment.
  - No significant improvement in nasal peak inspiratory flow rate.

Intranasal and 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.
  - e.g. Aukema AAC et al. JACI 2005;115:1017-23.
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.
Postoperative patient with NP prior to initiation of topical steroid irrigations
Same patient one month after initiation of topical steroid irrigations.
Anti-IL-5 as a treatment for nasal polyposis

Phase I, DBPCT involving 24 patients with bilateral NP

Treatment: a single IV injection of humanized antihuman-IL-5 (reslizumab) at a dose of 1 mg/kg, 3 mg/kg or placebo

Method: assessment of
- nasal polyp size at 4, 8 and 12 weeks
- symptom scores
- peripheral eosinophil counts and ECP
- peripheral and local IL-5 levels
- eotaxin levels

Anti-IL-5 treatment for nasal polyposis

- Results:
  - Blood eosinophils and ECP levels were reduced for 8 weeks
  - At 4 wks, NP were reduced in ½ of subjects treated with either dose of anti-IL-5 ("responders")
  - "Responders" had increased IL-5 concentrations in nasal secretions at baseline compared with nonresponders.
  - Effects of anti-IL-5 waned at 8 and 12 weeks
  - Placebo patients were unchanged or worse at all time points

**Anti-IL-5 treatment for nasal polyposis**

- RDBPCT of mepolizumab as Rx for subjects with NP “refractory” to corticosteroid therapy.
- Rx: mepolizumab (N = 20), 2 IV injections 28 days apart of 750 mg of mepolizumab, or placebo (N=10) over a 8 weeks.

**Results:**

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

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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.

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

Allergic fungal rhinosinusitis

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

Immunofluorescence stain of fungal hyphae

Hematoxylin/eosin stain

Allergic fungal rhinosinusitis
AFRS: oral steroid and oral antifungal studies

- **Oral steroid trials:**
  - Rupa V et al. (2010 Eur Arch Otorhinolaryngol 267: 233.)
  - Prednisone 50 mg/day x 6 weeks, followed by 6 weeks of tapering, or placebo.
  - All patients also received itraconazole 200 mg daily for 12 weeks.
  - 8 of 12 patients who received prednisone and 1 of 12 patients who received placebo were disease free at 12 weeks (p = 0.009).

- **Oral antifungal trials:**
  - Rupa (2010)
  - (as above)

  - 12-year retrospective chart review of 139 patients meeting the AFS criteria: (atopy, radiographic findings, eosinophilic mucin, nasal polyposis, and positive fungal culture or stain).
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

**Antifungal for minimum of 3 months**

**Relatively short period of Rx with oral prednisone**

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

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

**+/- immunotherapy**
Allergy referral Immunotherapy as indicated
AFRS: antifungal use (clinical experience)

RESULTS:

Overall, 50.3% experienced recurrence, but reoperation was required in only 20.5% of 83 patients initially managed by our protocol. No serious adverse effects attributed to itraconazole.

CONCLUSION:

Use of itraconazole, short-burst low-dose oral corticosteroids, topical corticosteroids, and endoscopic surgery is safe and clinically effective in the management of AFS.

Medical management with itraconazole may reduce the need for oral corticosteroids and lessen the need for revision surgery.

Summary
(Allergy intervention is recommended in allergic subjects.)

- Adjunctive saline irrigations and intranasal steroids
- Combination antibiotic + oral steroid ("intensive medical therapy")
- Consider trial of long-term low dose macrolides
- Consider steroid sinus rinse in difficult cases

- **CRSsNP**
  - Oral steroids ("medical polypectomy")

- **CRSwNP**
  - Intranasal steroids can be effective
  - If intranasal steroid fails, steroid sinus irrigation should be tried

- **AFRS**
  - Oral steroids (stabilization, rapid tapering)
  - Oral itraconazole can be used safely and may reduce oral steroid need for reoperations
  - Steroid sinus irrigations in all cases
  - Immunotherapy is safe and may be beneficial