Endotypes in Chronic Rhinosinusitis

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Faculty Disclosures

• SDP Disclosure
  – None
Clinical Practice Guideline (Update): Adult Sinusitis Executive Summary

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Figure 1. Adult with possible sinusitis. Table numbers correspond to numbers in the full-length version of the guideline. 16

15 AAS, acute sinusitis; 16, acute bacterial sinusitis; 17, chronic rhinosinusitis without nasal polyps; 18, chronic rhinosinusitis with nasal polyps; 19, upper respiratory infection.
Chronic Rhinosinusitis

- Diagnosed based on clinical and objective findings (physical exam, endoscopy, CT findings)
- Leads to broad heterogeneity of patients diagnosed with a “single” clinical disorder
Phenotype

The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment

Phenotyping of CRS

Polyps vs. Without Polyps
Associated Conditions

- Asthma
  - AERD (Samter’s Triad)
  - EGPA/Churg-Strauss
- Cystic Fibrosis
- Allergic Fungal Rhinosinusitis
- Odontogenic Sinusitis
- Mycetoma

Phenotyping for Chronic Sinusitis

- Does this provide adequate categorization of CRS patients to select appropriate therapy?
- Are there other options?
Endotype

A subtype of a condition which is defined by a distinct functional or pathobiological mechanism

Who Cares?
Medical Treatment

- Corticosteroids
  - Topical
  - Systemic
- Antimicrobials
  - Antibiotics
    - Systemic
    - Topical
    - Macrolides
  - Antifungals
    - Topical
    - Systemic
- Other
  - ASA desensitization
  - Anti-leukotrienes
  - Anti IgE antibody (omalizumab)
  - Anti IL-5 antibody (mepolizamab, reslizumab, benralizumab)
  - Anti IL-4/13 (dupilumab)

Does Phenotype = Endotype?
Comparison of CRS Without and With Polyps

<table>
<thead>
<tr>
<th>CRS without Polyps</th>
<th>CRS with Polyps</th>
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<tbody>
<tr>
<td>• Interferon-gamma</td>
<td>• Eotaxins</td>
</tr>
<tr>
<td>• TGF-beta</td>
<td>• Eosinophilic cationic protein</td>
</tr>
<tr>
<td>• Pro-inflammatory cytokines</td>
<td>• IL-5</td>
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<tr>
<td>Th1-cytokine profile</td>
<td>• IgE</td>
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<tr>
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<td>Th2-cytokine profile</td>
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Patient #1

• 53M referred for chronic sinusitis
• New onset of persistent symptoms 13 months ago
  – Nasal congestion, thick nasal drainage, and hyposmia
  – Intermittent wheezing and cough on inhaled steroid treatment
• Negative allergy testing
• Temporary relief from oral steroids
Patient #1 – CRS, No Polyps

- Lower airway symptoms
- Late onset disease
- Response to oral steroids
- Negative allergy testing
- CT Findings

CT Scan
How can we Endotype patients?

• Operative Pathology
• Laboratory Evaluation
Phenotype – No Polyps

- Pathology: “Eosinophil-rich mucin and inflamed sinonasal mucosa”
- Cultures: Staph aureus
- No fungus seen on pathology or cultures

CRS with Polyps

- Eotaxins
- Eosinophilic cationic protein
- IL-5
- IgE
- Th2-cytokine profile

Clinical Implications

- High likelihood of recurrent inflammation
- Steroid responsive
- Good candidate for biologic treatment
FDA NEWS RELEASE

FDA approves first treatment for chronic rhinosinusitis with nasal polyps

For Immediate Release: June 26, 2019

WARNING!

Immunology Slide(s)
Patient #2

- 48 y/o Asian-American woman developed bilateral nasal congestion, PND, Cough, thick nasal drainage 1 year ago.
- Minimal change with steroids (oral and topical) and antibiotic treatment

Patient #2 – CRS with Polyps

- Persistent inflammation and early polyp recurrence following surgery
- No significant endoscopic improvement with topical or oral steroid treatment
- Cultures demonstrated MSSA, culture-directed antibiotics ineffective
- Pathology: Chronically inflamed sinonasal mucosa
Pathology

Phenotype – CRS With Polyps

- Pathology - Neutrophilic Infiltrate
- Normal eosinophil count and total IgE
Macrolide Treatment

- Non-eosinophilic polyps
- Non-steroid responsive
- Higher incidence in Asian Patients

Summary

- Chronic sinusitis is a heterogeneous disease
- Treatment approach and efficacy for CRS varies depending on CRS Subtype
- Emerging therapies require endotyping of CRS patients (not just phenotyping) to optimize treatment efficacy