Chronic rhinosinusitis with nasal polyps: new classification and treatment paradigms

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Immunology of CRS and treatment implications

Objectives

➢ To discuss the novel classification of chronic rhinosinusitis
➢ To review the immune dysfunction associated with CRS with nasal polyps with treatment implications
➢ To review spectrum of treatment options for CRS with nasal polyps

Clinical classification of CRS

➢ CRSsNP
➢ CRSwNP
  • AFRS/eosinophilic mucin rhinosinusitis
  • Cystic fibrosis
  • Aspirin exacerbated rhinosinusitis
CRSsNP
➢ 54 yo male presents with recurrent sinus infections
➢ CT sinus showed left maxillary sinus heterogeneous opacification

CRSwNP
➢ 54 yo female presents with recurrent sinus infections s/p prior FESS
➢ IgG subclass levels deficient

2020 Classification of primary CRS

- Localized (unilateral)
  - Type 2
  - Non-type 2
- Diffuse (bilateral)
  - Type 2
  - Non-type 2

AFRS
- Isolated sinusitis
- eCRS
- ACRS
- CCAD
- Non-eCRS

EPOS 2020
3 major effector immunity

**Type 1**
- Protect against intracellular microbes
- Activate mononuclear phagocytes
- ILC1 and T_h1
- IFN-γ

**Type 2**
- Protect against helminthes and venoms
- Activate mast cells, eosinophils, and basophils
- ILC2 and T_h2
- IL-4, IL-13 and IL-5

**Type 3**
- Protect against extracellular bacteria and fungi
- Activate neutrophils, phagocytes and epithelial antimicrobial responses
- ILC3 and T_h17
- IL-17 and IL-22

Allergic diseases, asthma and CRSwNP

**Immunology of CRS and treatment implications**

**Innate and Adaptive Immunity**

**Innate Immunity**
- Physical barriers
- Chemical barriers
- Cellular Defenses

**Adaptive Immunity**
- Active Immunity
  - Natural
  - Vaccination
- Passive Immunity
  - Maternal
  - Medical

**Mucus and mucociliary clearance**
- Composed primarily of macromolecules produced by MUC5AC and MUC5B
- Other components
  - Antimicrobial peptides
  - Immunoglobulins – IgA
  - Enzymes
  - Opsonins
- Cells responsible for mucus production
  - Goblet cells, serous cells, epithelial cells, other cells with mucosa
Cystic fibrosis

- Healthy: Watery mucus moved quickly by mucociliary clearance
- Cystic Fibrosis: Thick and viscous mucus moved very slowly trapping bacteria

Secreted antimicrobial peptides in sinus mucus

- Defensins
- Cathelicidins (LL-37)
- Histatins
- Elastase inhibitors (SLPI)
- C-type lectins
- Lactoferrin
- Lysozyme
- Chitinases
- Opsonins
- Lipocalins

Histatin gene expression down regulated in allergic fungal rhinosinusitis

Tyler M et al, Otolaryngol Head Neck Surg, July 2018
Bitter taste receptors in CRS

Hamilos DL, JACI, 2015

Epithelial cell barrier function

Tight junctions
- Regulate transport of solutes and ions across epithelia

Adherens junctions
- Mediate cell-to-cell adhesions and promote formation of tight junctions

Disruption of tight junctions increases permeability and reduces transepithelial resistance

Innate effector cells

Neutrophils

Eosinophils

Mast cells

Innate lymphoid cells


Spectrum of clinical presentation of CRS can be linked to different dysfunctions in the innate immune response.
Antibody deficiencies most common immunodeficiency in CRS

- 3 antibody immunodeficiencies
  - Selective IgA deficiency
  - Common variable immunodeficiency
  - Specific antibody deficiency
- Prevalence in CRS patients screened for immunodeficiencies
  - CVID 5%
  - Specific antibody deficiency 24%

Dysfunctional adaptive immune response in CRSwNP

- Increase activated B cells and auto-reactive antibodies
- Elevated mucosal levels of autoreactive IgG and IgA to nuclear antigens and basement membrane components found in CRS
- Levels associated with local IgE levels and disease severity
- Presence of tertiary lymphoid organs in CRS sinonasal mucosa -> increase activated B cells

Take home message on adaptive immunity in CRS

- CRSsNP - immunodeficiencies
- CRSwNP - hyper adaptive immune response
Immunology of CRS and treatment implications

Glucocorticoids

<table>
<thead>
<tr>
<th></th>
<th>Pros</th>
<th>Cons</th>
</tr>
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<tbody>
<tr>
<td>Oral steroids</td>
<td>Potent effect</td>
<td>Effective vs. mucus</td>
</tr>
<tr>
<td>Nasal steroid sprays</td>
<td>Meta and systemic analysis consistently support efficacy</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Steroid saline irrigations</td>
<td>Incorporates irrigations</td>
<td>Only 3-4% solution remains in sinuses</td>
</tr>
<tr>
<td>Steroid drops</td>
<td>Relatively concentrated dose</td>
<td>Challenging to administer correctly</td>
</tr>
<tr>
<td>Steroid eluting stents</td>
<td>High concentration of delivered steroids locally</td>
<td>Uneven delivery</td>
</tr>
<tr>
<td>Exhalation Delivery (Xhance)</td>
<td>Deeper penetration</td>
<td>Cost</td>
</tr>
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</table>

Glucocorticoids: Topical, Systemic

Tips for CRSwNP:
- Oral steroids: Potent effect, effective vs. mucus, weight gain
- Nasal steroid sprays: Meta and systematic analysis, consistent support efficacy
- Steroid saline irrigations: Incorporates irrigations, only 3-4% solution remains in sinuses
- Steroid drops: Relatively concentrated dose, challenging to administer correctly
- Steroid eluting stents: High concentration of delivered steroids locally, uneven delivery
- Exhalation Delivery (Xhance): Deeper penetration, cost

Implications on Treatment Options for CRSwNP
Steroid eluting device

- 370 mcg over 14 days
- 1350 mcg over 90 days

- Placed in post-op ethmoid cavity
- All published RCTs met primary endpoints
- FDA approved for CRSwNP

LYR-210 steroid eluting implant with positive Phase 2 RCT results

- Nasal implant loaded with 7500 mcg mometasone delivers stable dose over at least 6 months
- Placed in-office under local in middle meatus, even in CRS patients with no prior sinus surgery
- Reported topline results – Dec 7
  - SNOT-22: drop in 19 points more in treatment vs control at 6 months
  - No treatment related serious events
- Planning Phase 3 trial now

Fluticasone exhalation delivery system - Xhance®

- 4 large clinical trials (2 DBRCT which included 650 CRS patients) support efficacy
- Range of 20 point improvement in SNOT 22 over placebo at 16 weeks
- 56 – 72% pts noted to have at least 1 pt improvement in polyp score at 16 weeks
- 93 mcg/spray fluticasone propionate
Biologics – the shiny new treatment option for CRSwNP

Dupilumab – FDA approved in US for CRSwNP June 2019

- ≥18 yrs old w/ bil NP
- NPS ≥ 5
- Mometasone 100 ug BID
- Excluded AFRS

<table>
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<tr>
<th>Liberty SINUS 24</th>
<th>Liberty SINUS - 52</th>
<th>Total</th>
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<tbody>
<tr>
<td>Placebo (n=153)</td>
<td>Placebo (n=153)</td>
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</tr>
<tr>
<td>Dupilumab q2w (n=153)</td>
<td>Dupilumab q2w-q4w (n=150)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70 (53%)</td>
<td>88 (62%)</td>
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<tr>
<td>Female</td>
<td>63 (47%)</td>
<td>85 (60%)</td>
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<tr>
<td>Bil NPS</td>
<td>5.86</td>
<td>5.64</td>
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<tr>
<td>Asthma</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>AERD</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>96 (62%)</td>
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Bachert et al, Lancet 2019

Co-primary endpoint at 24 weeks
Co-primary endpoint at 24 weeks

Bachert et al., Lancet 2019

### Other biologics in pipeline or available for asthma

<table>
<thead>
<tr>
<th>Biologic agent</th>
<th>Action</th>
<th>Effect</th>
<th>Status</th>
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<tbody>
<tr>
<td>Reslizumab</td>
<td>IgG4 mAb</td>
<td>Anti-IL-5</td>
<td>FDA approved for ≥ 18 yrs severe asthma – March 2016</td>
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<tr>
<td>Mepolizumab</td>
<td>IL-5 antagonist</td>
<td>Induce apoptosis of eosinophils and reduce local tissue recruitment of eosinophils</td>
<td>FDA approved for ≥ 5 yrs eosinophilic severe asthma and Chronic Sinusitis – SINUSITIS TPS: &lt;0.73</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL-5Rα</td>
<td>Reduce recruitment of eosinophils</td>
<td>FDA approved for ≥ 12 yrs eosinophilic severe asthma</td>
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<tr>
<td>Omalizumab</td>
<td>Anti-IgE</td>
<td>Decrease cell bound IgE levels and decrease mast cell degranulation</td>
<td>Approved for allergic rhinitis and allergic asthma</td>
</tr>
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Typical experience with dupilumab

Biologics in CRS management

**Pros**
- Presents possible precision treatment
- Offers treatment options to recalcitrant CRS patients
- Associated with some dramatic responses

**Cons**
- Cost
- Not curative
- Unknown long-term side effects of manipulating immune response
- Lack of biomarkers to identify responders
- Some require IV infusion

Conclusion
- Spectrum of clinical presentation of CRS can be linked to different dysfunctions in the innate and adaptive immune response
- CRS is a chronic inflammatory disease and steroids remain cornerstone
- Molecular understanding of the pathophysiology of CRSwNP is expanding with introduction of potential therapeutic targets
- Biologics may be justified in severe CRSwNP, especially in those with other Type 2 comorbidities