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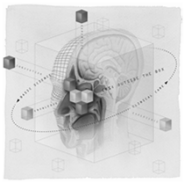

Chronic rhinosinusitis with nasal polyps: new classification and treatment paradigms

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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

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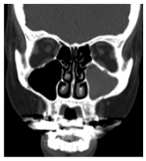
CRSsNP

- 54 yo male presents with recurrent sinus infections
- CT sinus showed left maxillary sinus heterogenous opacification

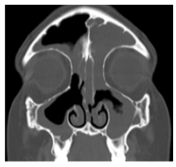


VS

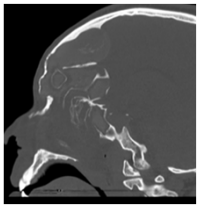
- 57 yo female presents with recurrent sinus infections s/p prior FESS
- IgG subclass levels deficient

CRSwNP

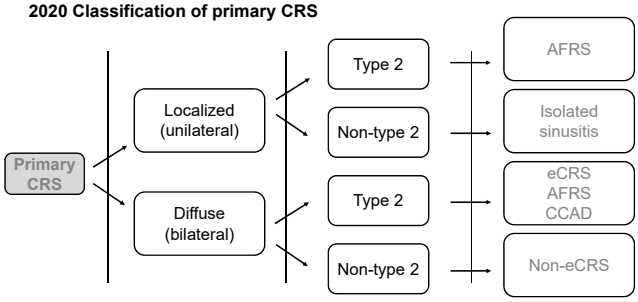
- 28 yo female with asthma and sensitivity to aspirin presents with recurrent nasal polyps



VS



2020 Classification of primary CRS



EPOS 2020

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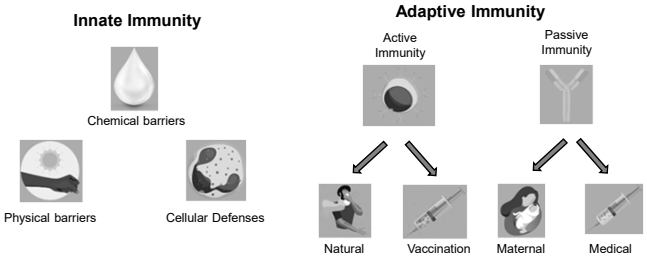
3 major effector immunity

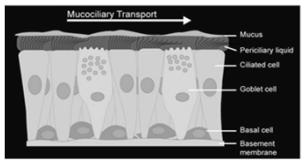
Type 1	Type 2	Type 3
• Protect against intracellular microbes	• Protect against helminthes and venoms	• Protect against extracellular bacteria and fungi
• Activate mononuclear phagocytes	• Activate **mast cells**, **eosinophils**, and basophils	• Activate neutrophils, phagocytes and epithelial antimicrobial responses
• ILC1 and T_H1	• ILC2 and T_H2	• ILC3 and T_H17
• IFN-γ	• **IL-4**, IL-13 and **IL-5**	• IL-17 and IL-22
	Allergic diseases, asthma and CRSwNP	CRS

Innate and Adaptive Immunity



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



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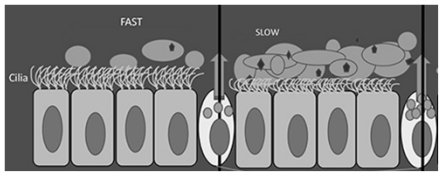
Cystic fibrosis

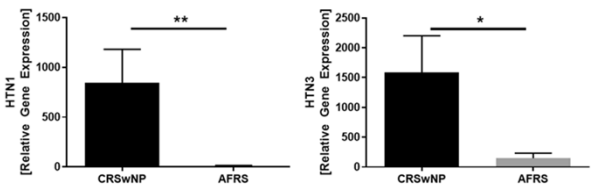
Healthy	Cystic Fibrosis
Watery mucus moved quickly by mucociliary clearance	Thick and viscous mucus moved very slowly trapping bacteria



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

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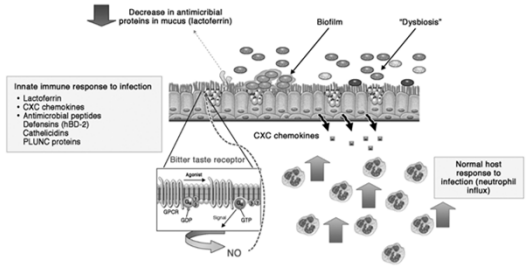
Bitter taste receptors in CRS



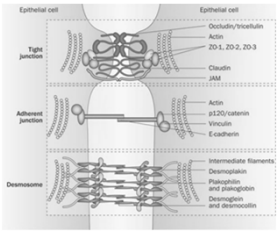
Hamilos DL, *JACI*, 2015

Epithelial cell barrier function

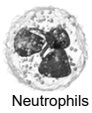
Tight junctions
- Regulate transport of solutes and ions across epithelia

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

Disruption of tight junctions increase permeability and reduces transepithelial resistance

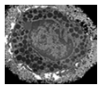


Innate effector cells



Neutrophils

Eosinophils



Mast cells

Increased percentage of mast cells within sinonasal mucosa of chronic rhinosinusitis with nasal polyp patients independent of atopy

Joanne L. Shaw, PhD[1,2], Faramarz Ashoori, MD, PhD[3], Samer Fakhri, MD[3], Martin J. Citardi, MD[3], Amber Luong, MD, PhD[1,2]

Understanding the Role of Neutrophils in Refractoriness of Chronic Rhinosinusitis With Nasal Polyps

Feng Lan,[1,2] Luo Zhang[1,2]*

Innate lymphoid cells

IL-33–Responsive Innate Lymphoid Cells Are an Important Source of IL-13 in Chronic Rhinosinusitis with Nasal Polyps

Joanne L. Shaw[1,2], Samer Fakhri[3], Martin J. Citardi[3], Paul C. Porter[1,2], David B. Corry[1,2], Farrah Kheradmand[1,2], Yong-Jun Liu[1], and Amber Luong[1,2]

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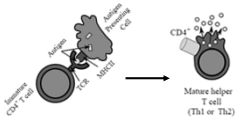
Take home message on innate immunity in CRS

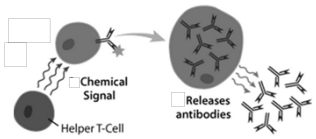
Spectrum of clinical presentation of CRS can be linked to different dysfunctions in the innate immune response

Cellular components of the adaptive immune response

T cells

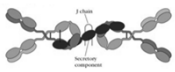


B cells



Types of immunoglobulins

- IgD
  - Trace amounts
- IgM
  - 10% of serum immunoglobulins
  - pentamer
- IgG
  - Most abundant isotype (75%)
  - Only isotype that can pass through human placenta
- IgA
  - 15% total serum immunoglobulins, but predominates in body secretions
  - Exist as monomer and dimer
- IgE



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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 immunodeficiences
  - 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

Tan BK et al, *JACI*, 2018

Take home message on adaptive immunity in CRS

CRSsNP - immunodeficiencies

CRSwNP - hyper adaptive immune response

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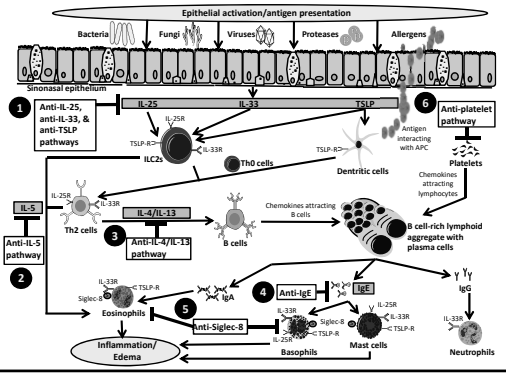
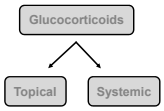


Implications on Treatment Options for CRSwNP




Glucocorticoids



	Pros	Cons
Oral steroids	Potent effect	Effectiveness wanes Significant side effects Weight gain
Nasal steroid sprays	Meta and systematic analysis consistently support efficacy	Limited sinus penetration Limited effectiveness with severe polyps
Steroid saline irrigations	Incorporates irrigations	Only 3-5% solution remains in sinuses
Steroid drops	Relatively concentrated dose	Challenging to administer correctly
Steroid eluting stents	High concentration of delivered steroids locally Bypass compliance issues	Uneven delivery Cost Repeat administration typical
Exhalation Delivery (Xhance)	Deeper penetration	Cost

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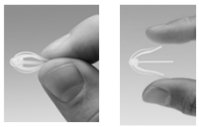
Steroid eluting device

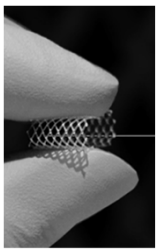


370 mcg over 14 days

1350 mcg over 90 days

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

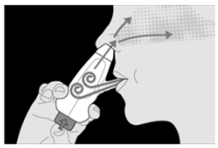
LYR-210 steroid eluting implant with positive Phase 2 RCT results



- 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



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Biologics – the shiny new treatment option for CRSwNP

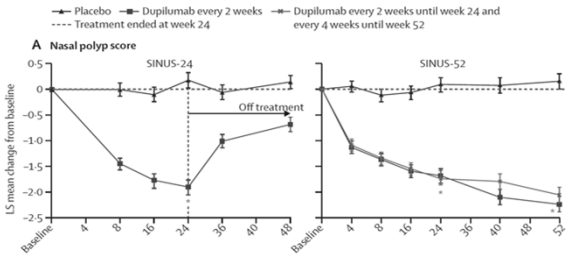
Dupilumab – FDA approved in US for CRSwNP June 2019

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

	Liberty SINUS 24		Liberty SINUS - 52			Total
	Placebo (n=133)	Dupilumab q2w (n=143)	Placebo (n=153)	Dupilumab q2w-q4w (n=145)	Dupilumab q2w (n=150)	n=724
Sex						
Male	70 (53%)	88 (62%)	95 (62%)	87 (60%)	97 (65%)	437 (60%)
Female	63 (47%)	55 (38%)	58 (38%)	58 (40%)	53 (35%)	287 (40%)
Bil NPS	5.86	5.64	5.96	6.29	6.07	5.97
Asthma	79	82	98	99	96	449 (62%)
AERD	38	46	44	41	35	204 (28%)

Bachert et al, *Lancet* 2019

Co-primary endpoint at 24 weeks



Bachert et al, *Lancet* 2019

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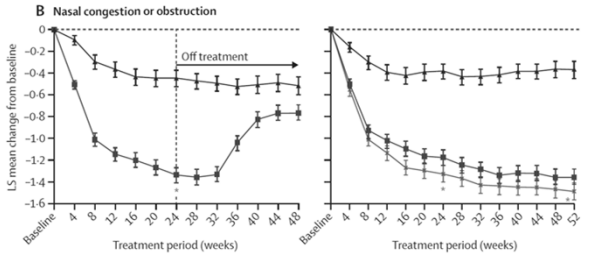
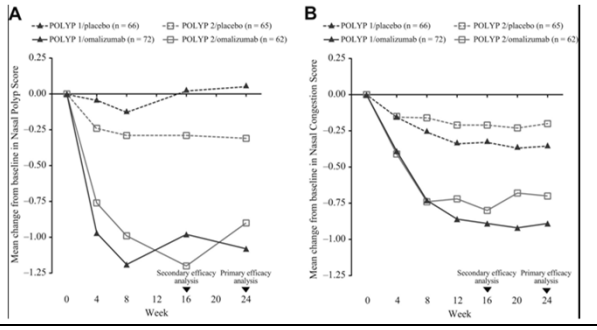
Co-primary endpoint at 24 weeks



Bachert et al, *Lancet* 2019

Other biologics in pipeline or available for asthma

Biologic agent	Action	Effect	Status
Reslizumab	IgG4 mAb Anti-IL5	Induce apoptosis of eosinophils and reduce local tissue recruitment of eosinophils	• FDA approved for > 18yrs severe asthma – March 2016 • BREATH trials completed
Mepolizumab	IL-5 antagonist	Induce apoptosis of eosinophils and reduce local tissue recruitment of eosinophils	• FDA approved for > 6yrs eosinophilic severe asthma and Churg-Strauss • SYNAPSE: TPS -0.73
Benralizumab	IL-5Rα	Reduce recruitment of eosinophils	• FDA approved for >12 yrs eosinophilic severe asthma • Completed Phase 3 trial
Omalizumab	Anti-IgE	Decrease cell bound IgE levels and decrease mast cell degranulation	• Approved for allergic rhinitis and allergic asthma • POLYP1 and 2: TPS -1.14 and -0.59



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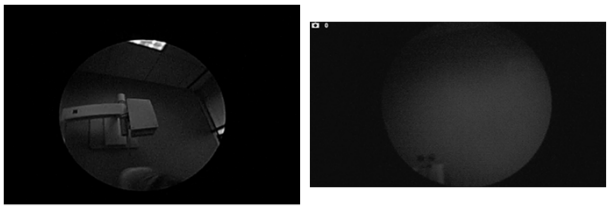
Typical experience with dupilumab



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