Chronic Rhinosinusitis with Nasal Polyposis

MUHC Center of Excellence for Atopic Dermatitis
A-Topics Lecture Series

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Clinical Case: P.A

- ID: 50 Female
- PMH: Asthma, AERD (failed ASA desensitization)
- All: NSAIDs
- Rx: Flovent, Singulair, Pulmicort rinses/drops, Prednisone
- PSH: Functional Endoscopic Sinus Surgery (FESS) 2012
- HPI: Ongoing nasal congestion, thick mucus discharge and hyposmia
- Asthma recently getting worse
- Lab: Eosinophils 0.8 (Normal 0-0.5), Total serum IgE 121

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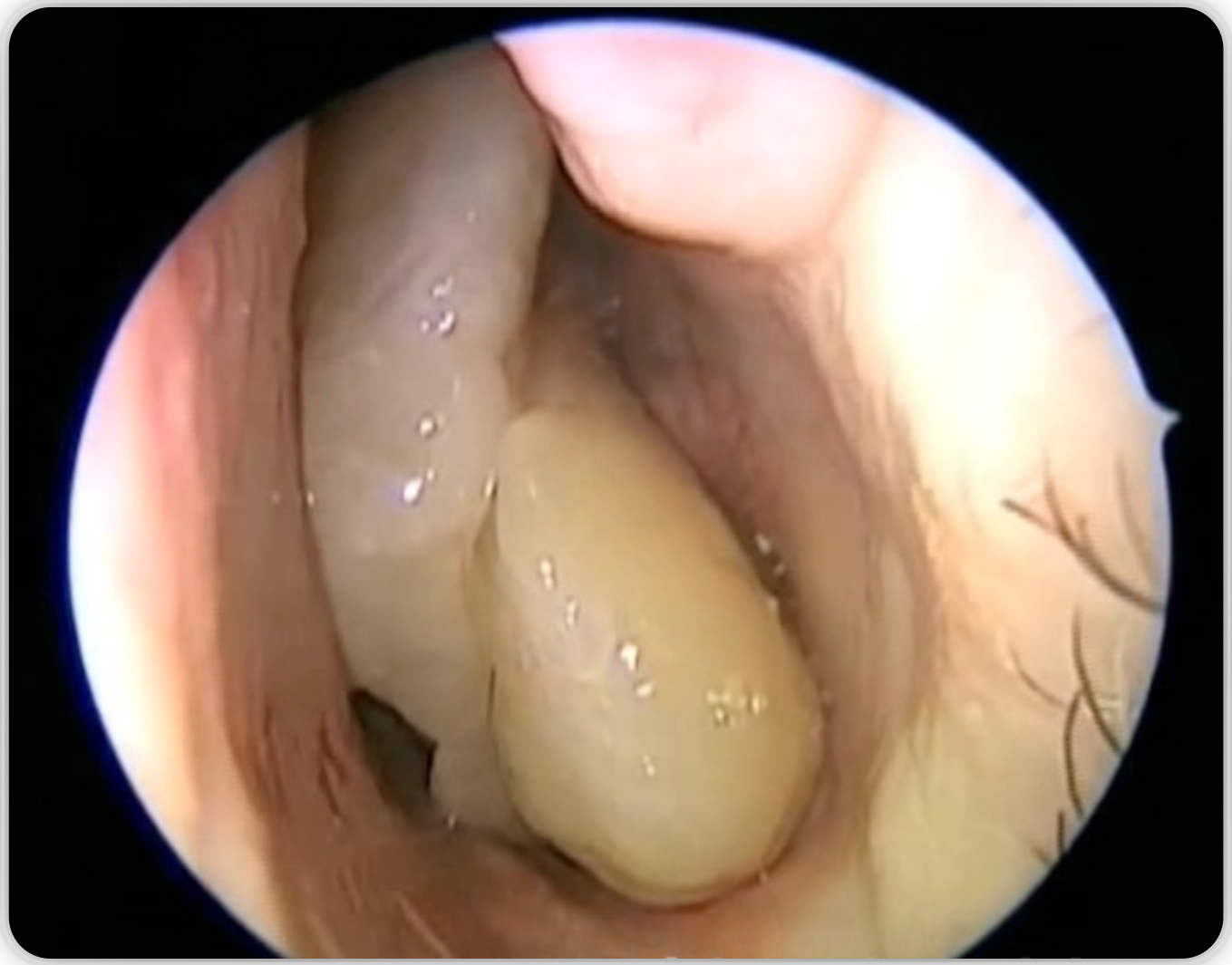

Sinoscopy

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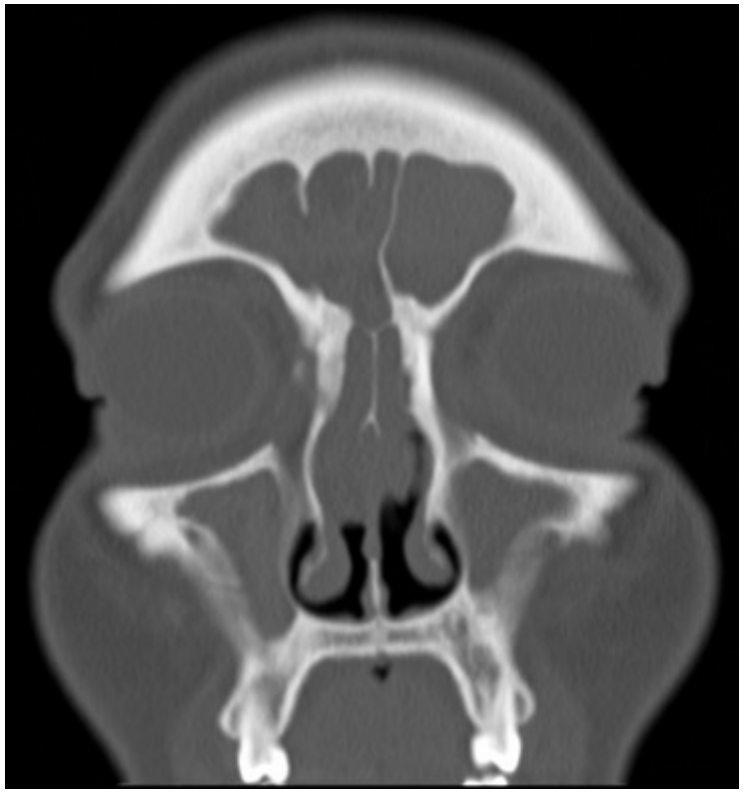
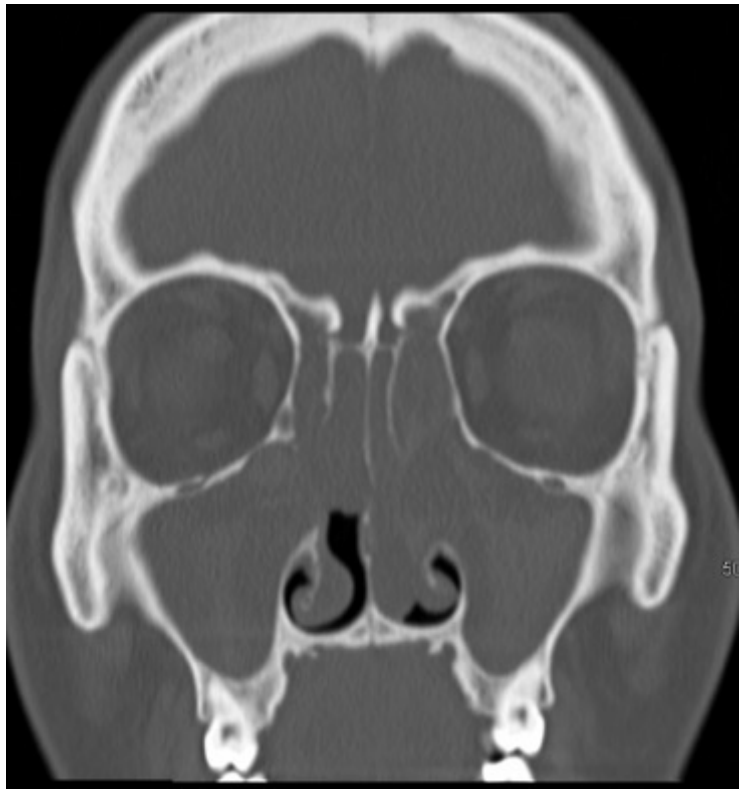
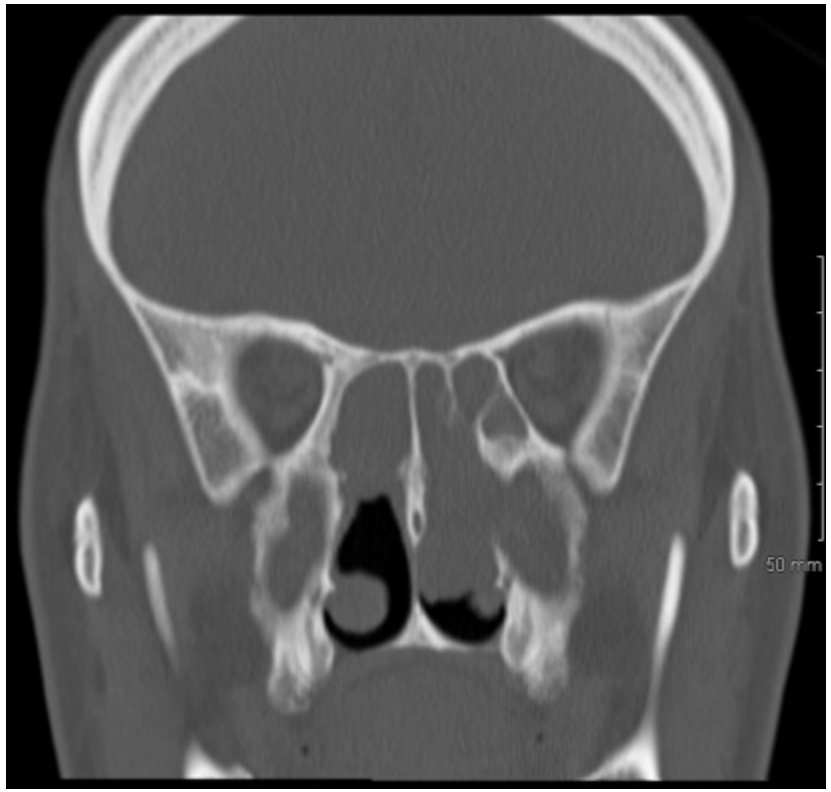
CT SINUS







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Burden of Nasal Polyps

- Among all patients with CRS, approximately 20–30% have CRSwNP.
- Worldwide prevalence of nasal polyps is estimated to be 1–4%
- The frequency of nasal polyps in the US is estimated to be 4.2%
- The impact of CRSwNP on overall HRQoL has been reported to be comparable with other chronic diseases such as COPD, asthma, and diabetes[6,7].

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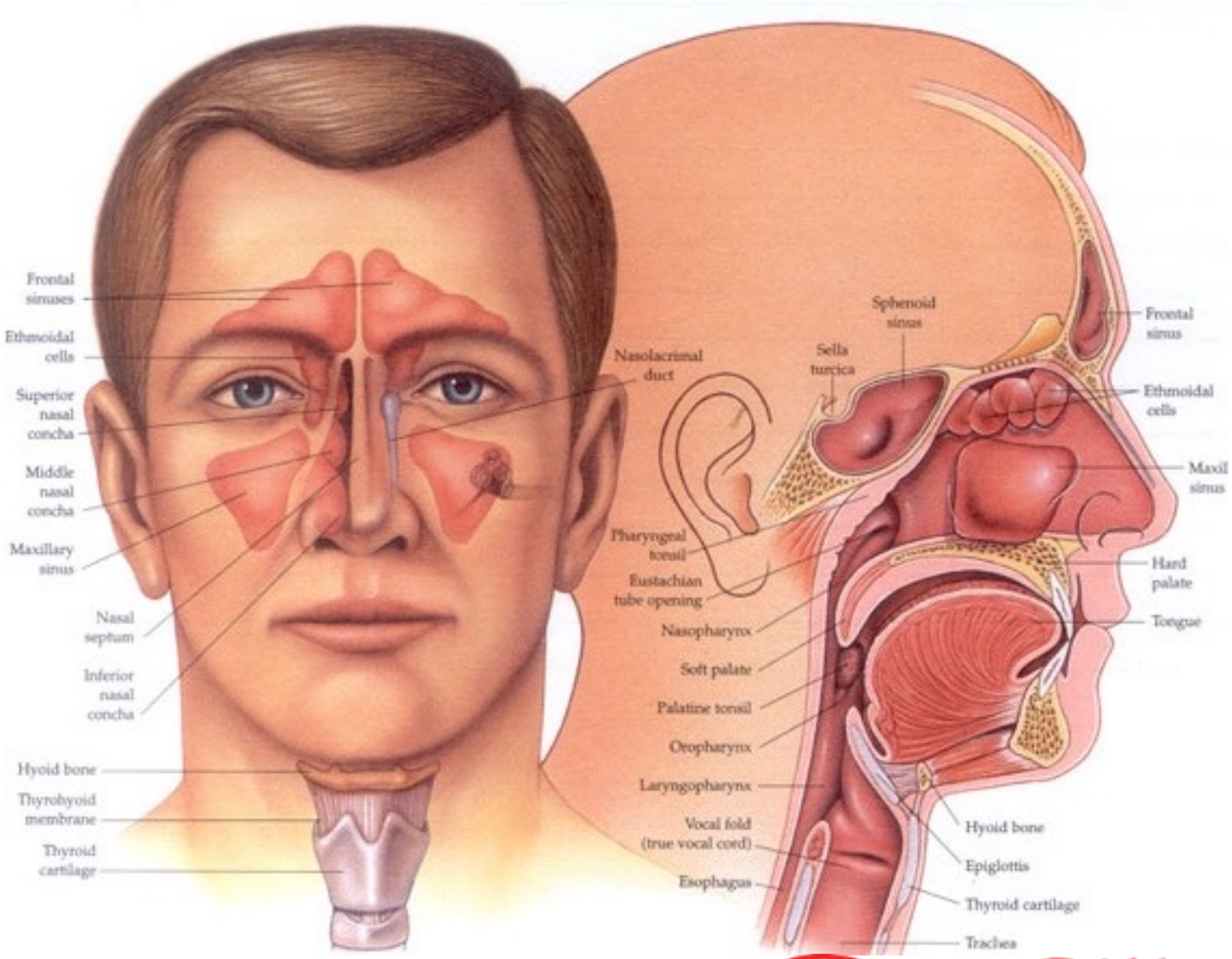
First, lets take a step back…

Paranasal Sinuses

- Mucosa lined air spaces within the bones of the face and skull

- 4 paired sinuses:
  - Maxillary
  - Ethmoid
    - Anterior & Posterior
  - Sphenoid
  - Frontal



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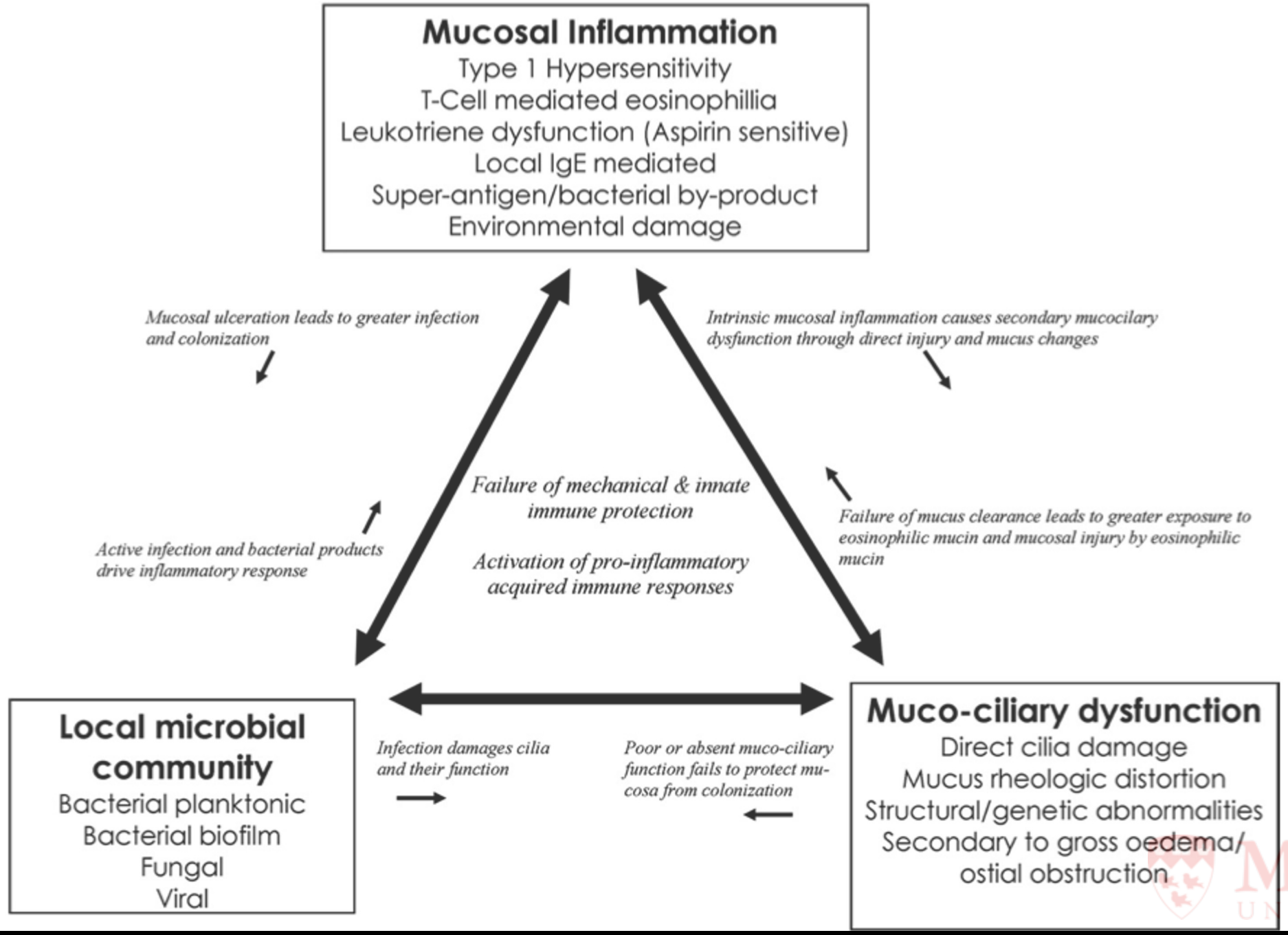
Mucosal Inflammation
Type 1 Hypersensitivity
T-Cell mediated eosinophillia
Leukotriene dysfunction (Aspirin sensitive)
Local IgE mediated
Super-antigen/bacterial by-product
Environmental damage
Mucosal ulceration leads to greater infection and colonization
Intrinsic mucosal inflammation causes secondary mucocilary dysfunction through direct injury and mucus changes
Failure of mechanical & innate immune protection
Activation of pro-inflammatory acquired immune responses
Active infection and bacterial products drive inflammatory response
Failure of mucus clearance leads to greater exposure to eosinophilic mucin and mucosal injury by eosinophilic mucin
Local microbial community
Bacterial planktonic
Bacterial biofilm
Fungal
Viral
Infection damages cilia and their function
Poor or absent muco-ciliary function fails to protect mucosa from colonization
Muco-ciliary dysfunction
Direct cilia damage
Mucus rheologic distortion
Structural/genetic abnormalities
Secondary to gross oedema/ ostial obstruction

Chronic Rhinosinusitis: Subtypes

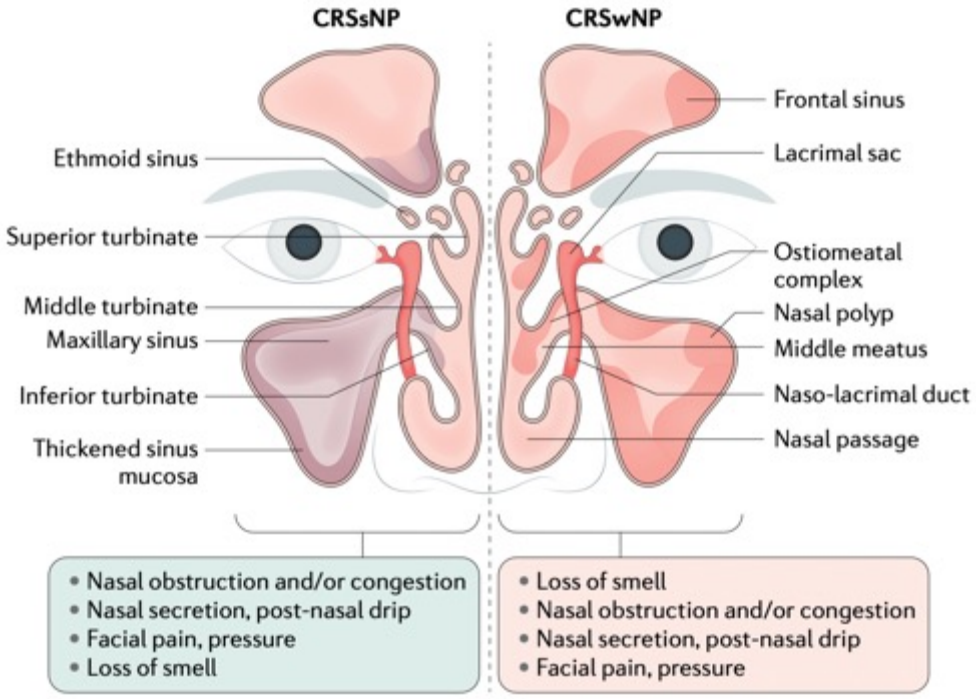

Fig. 1 | **Anatomy of the paranasal sinuses and the nasal passage.** Anatomical changes in chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) are demonstrated.

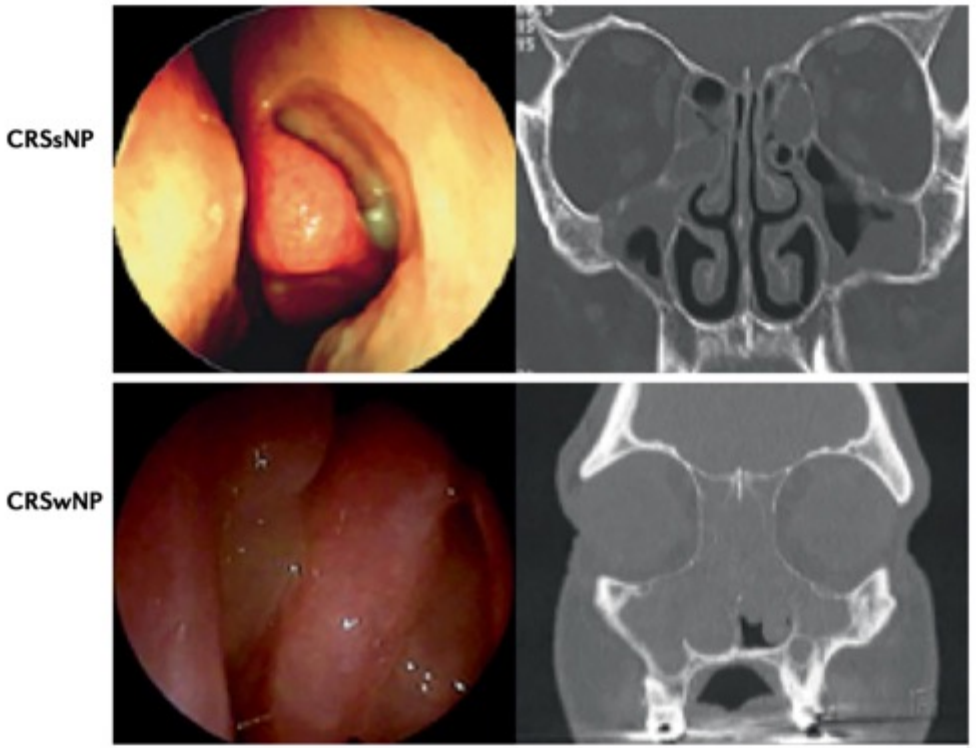

Fig. 6 | **Nasal endoscopy and CT scans to differentiate CRS phenotypes.** Typical endoscopic and radiological findings in chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusi

Bachert C, Marple B, Schlosser RJ et al. Adult chronic rhinosinusitis. Nat Rev Dis Primers. 2020 Oct 29;6(1):86.

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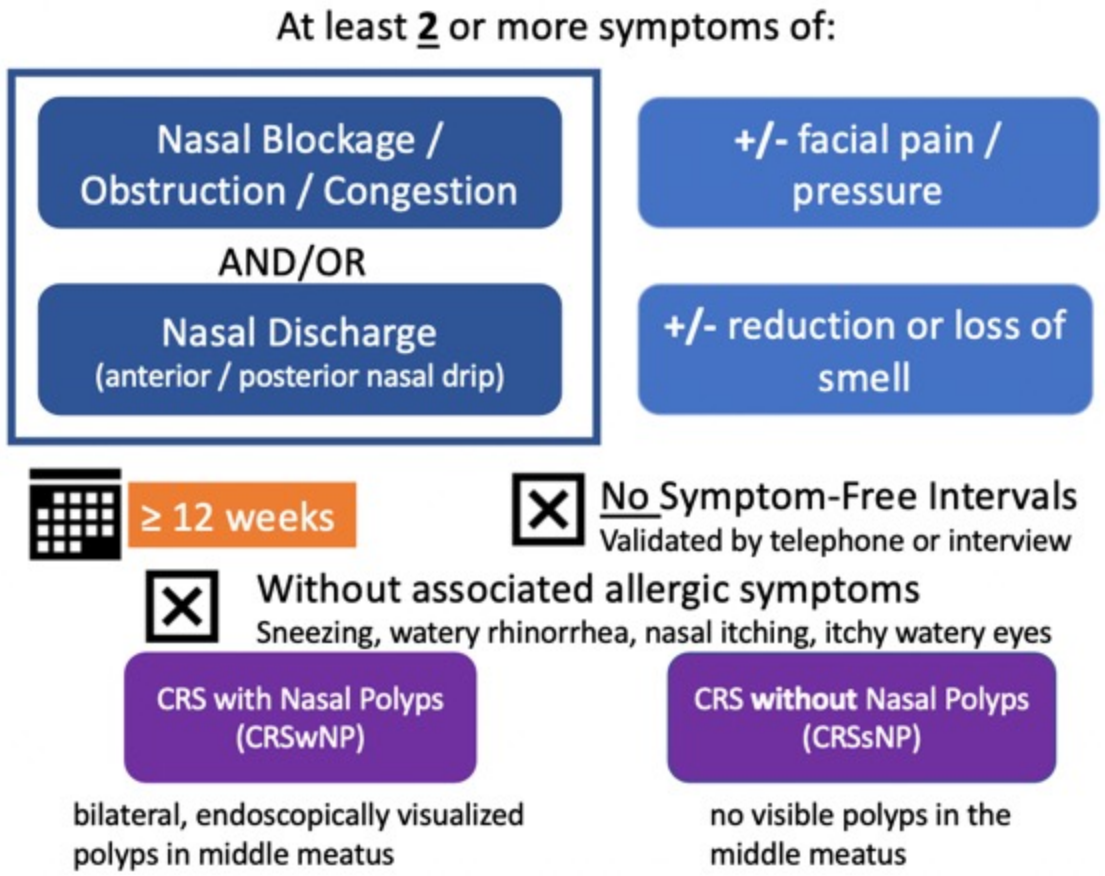
Definition: EPOS 2020



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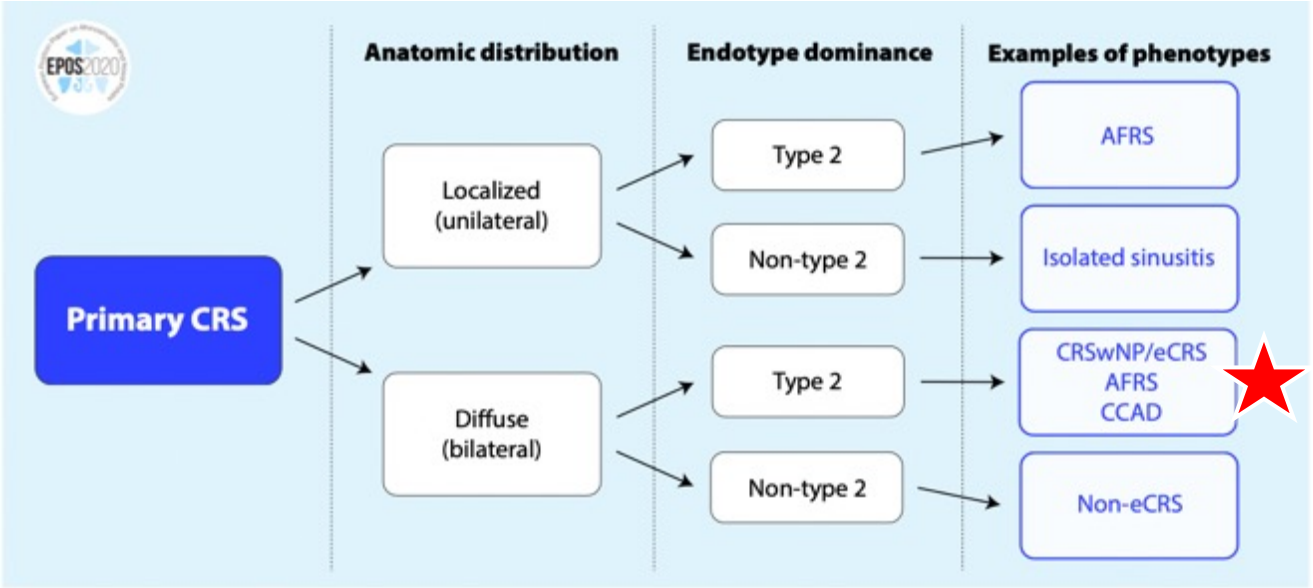
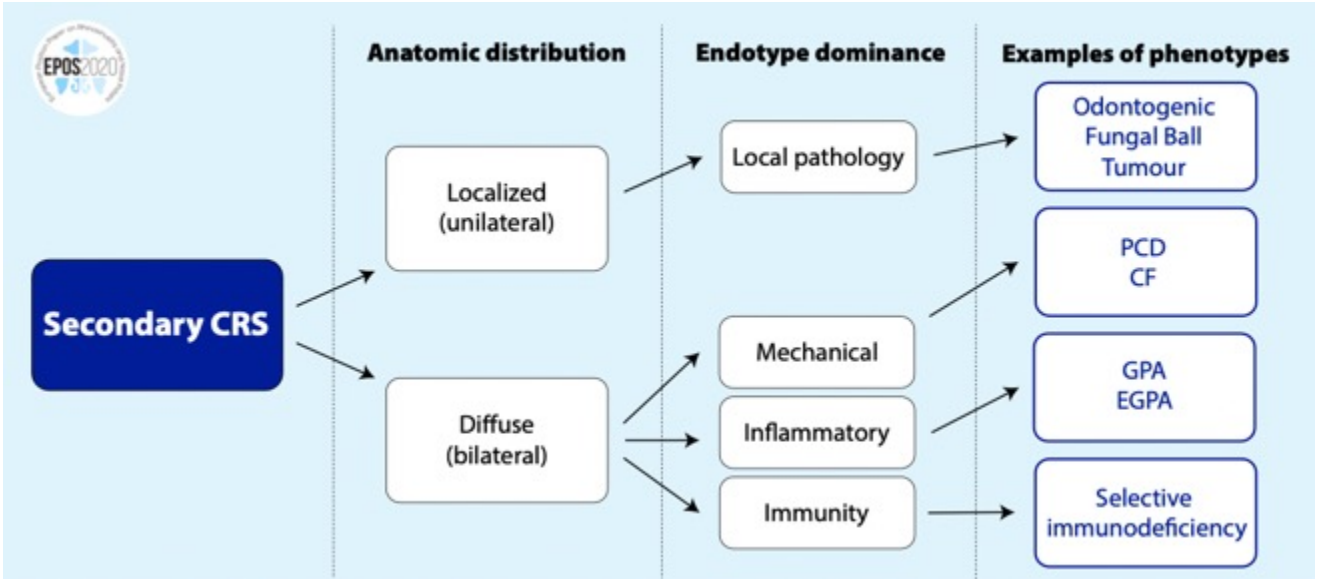
Fokkens WJ, Lund VJ, Hopkins et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464.

CRS Classification= Endotype + phenotype





Management Approach to CRSwNP

Appropriate medical therapy (AMT)

- Nasal steroid (drops / spray / rinses)
- Saline rinses
- Educate technique / compliance
- Consider OCS

6 – 12 weeks

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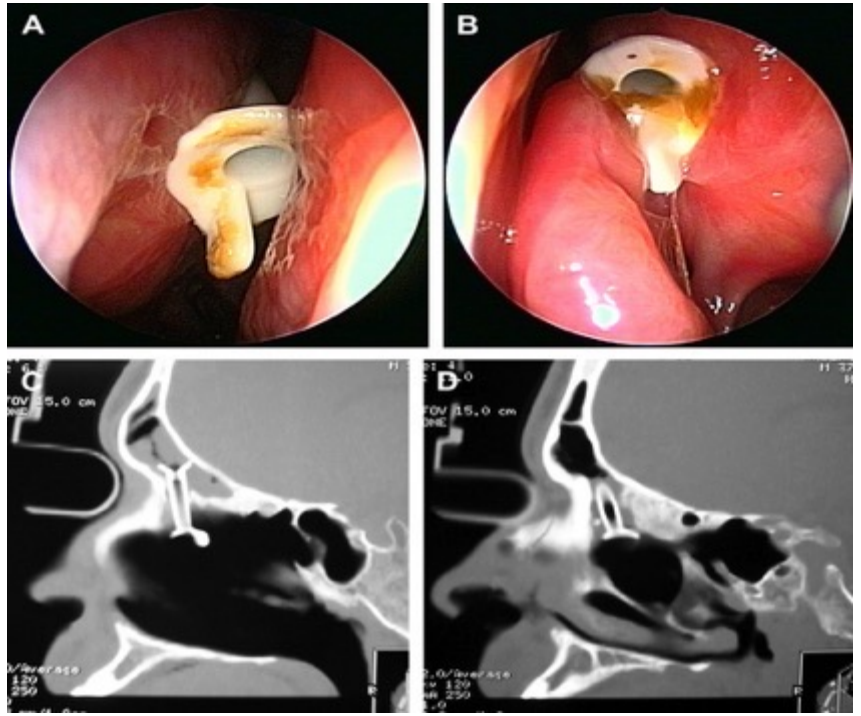
Topical Steroids Delivery

- Steroid sprays or irrigations
- Steroids-Eluting Nasal stents



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Oral Corticosteroids (OCS)

- Oral prednisone
- Typically 30mg taper over 21 days
- Effective in decreasing polyp size/number and improving symptoms
- Risk of systemic adverse events especially with long-term use
  - Cataracts, gastric upset, increase in intraocular pressure, reduced bone mineral density, HPA suppression and thinning of the skin

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Management Approach to CRSwNP

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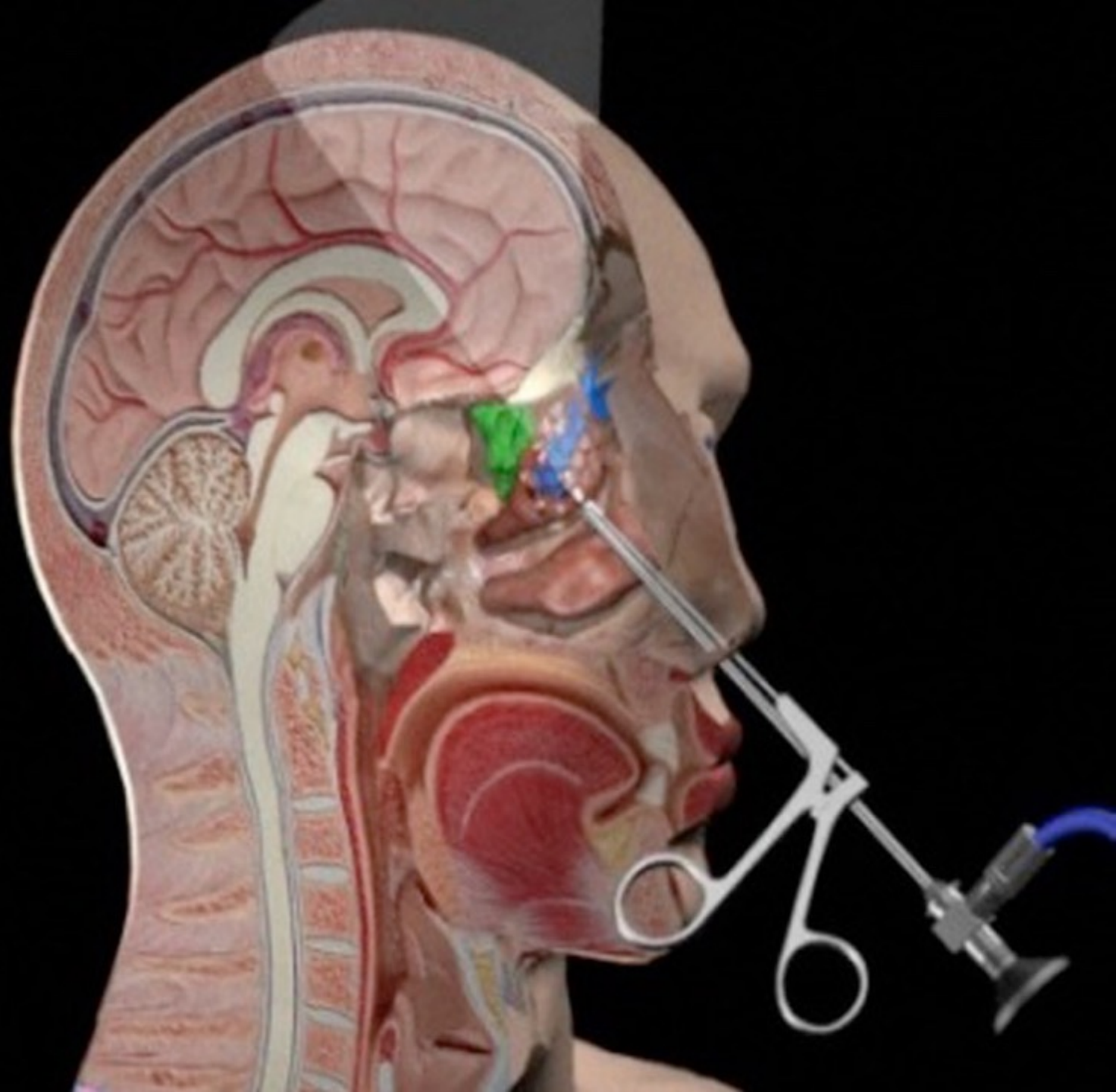
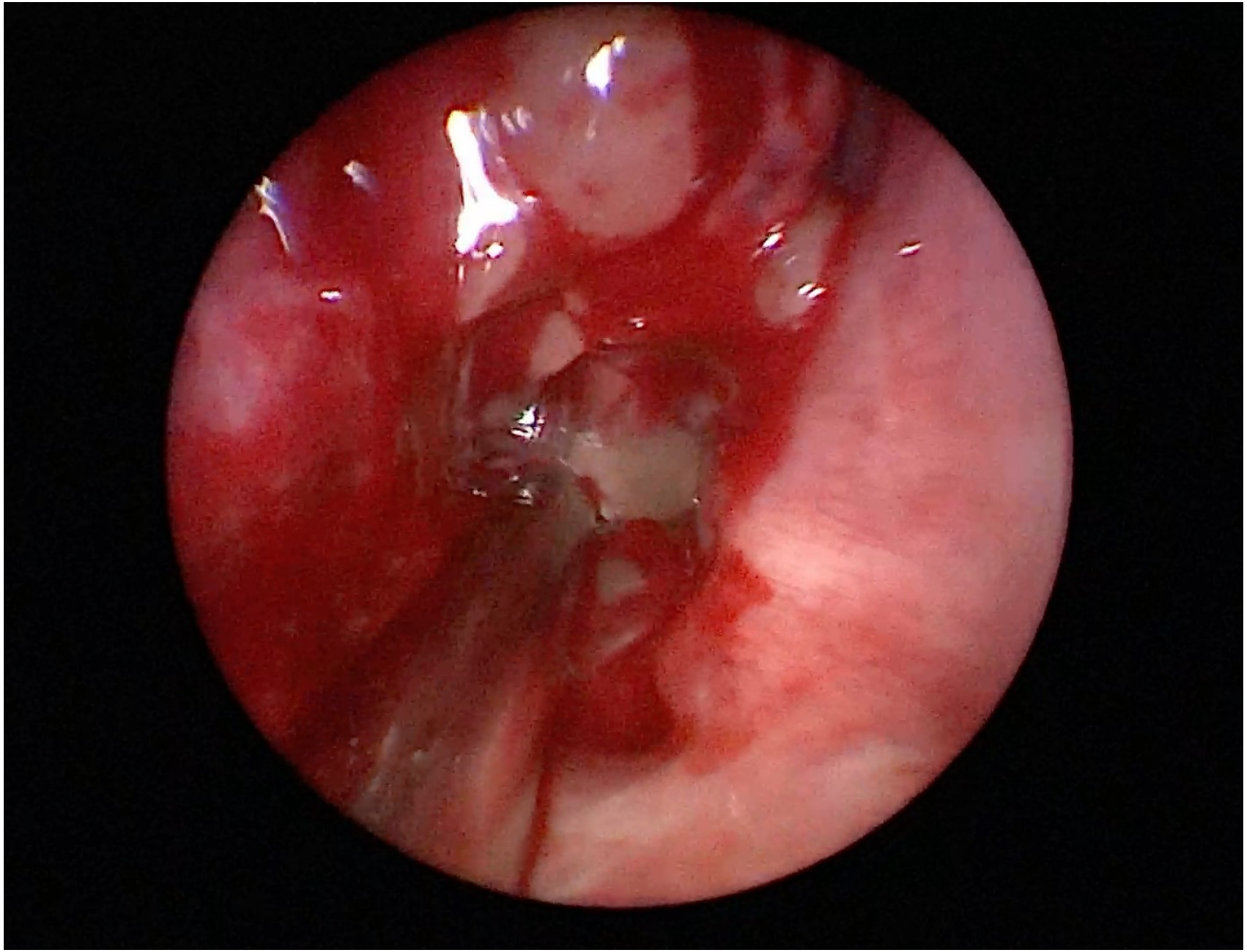
Endoscopic Sinus Surgery

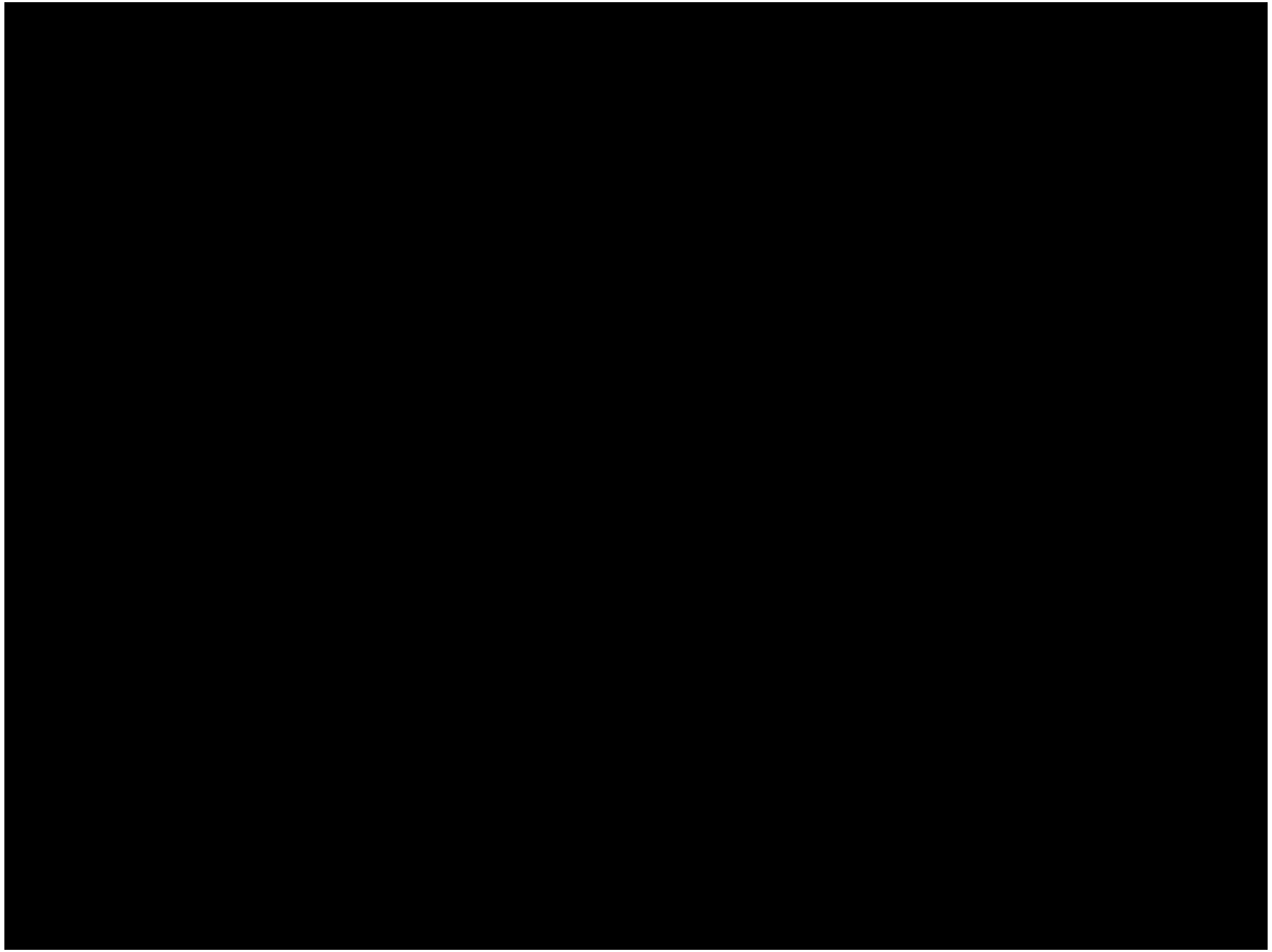
- Minimally invasive surgical technique
- Diseased or obstructing tissue removed from sinuses with the goal of improving or restoring normal sinus function
- Use of Hopkins rod telescopes to aid in the visualization of the nose and sinus cavities
- Generally avoids the need for external incisions

Goals of Sinus Surgery

- Creates a sinus cavity that incorporates the natural ostium.
- Allows adequate sinus ventilation.
- Facilitates mucociliary clearance.
- Facilitates instillation of topical therapies.

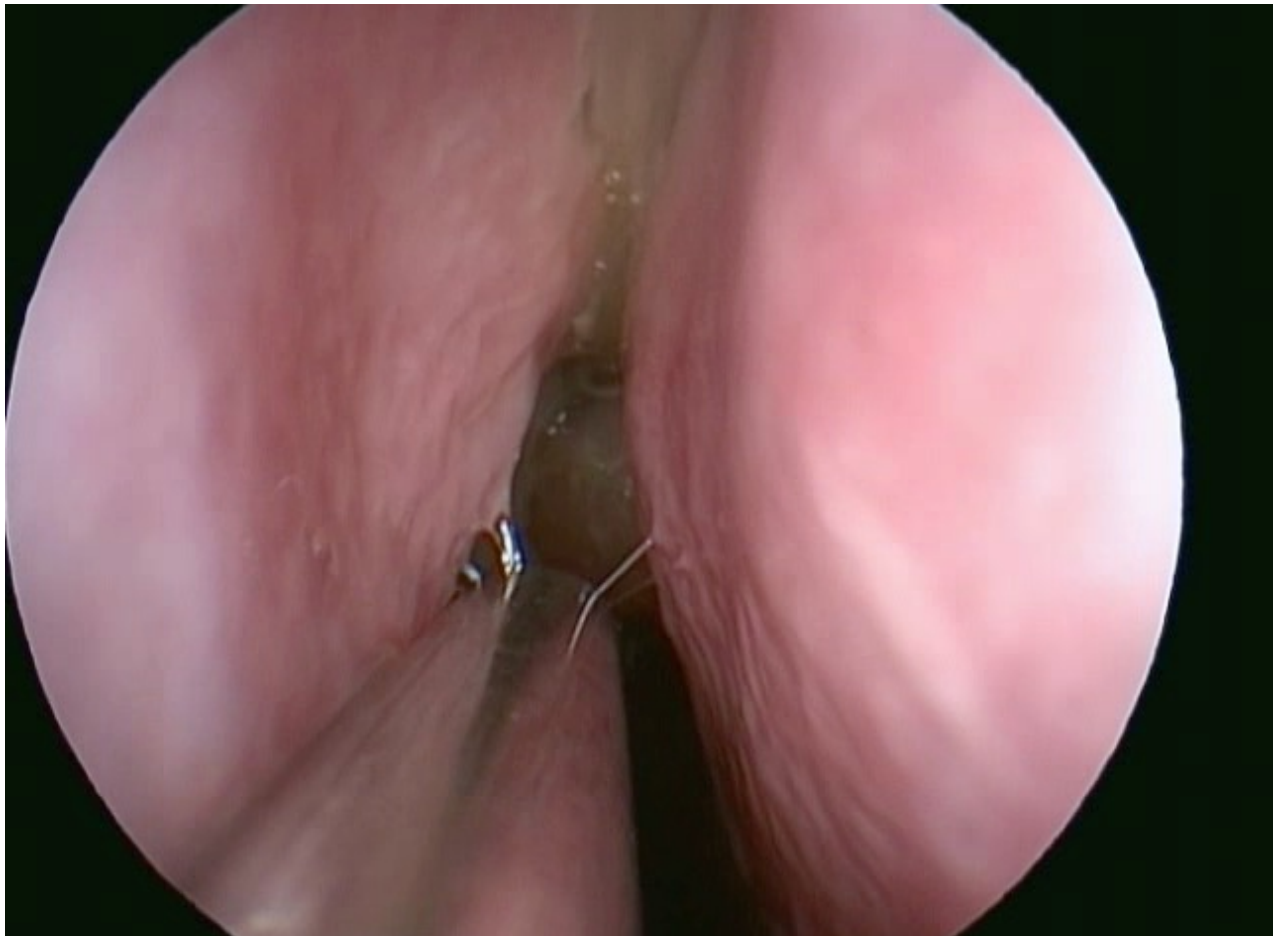






Ideal surgical outcome

ASA Triad



Management Approach to CRSwNP

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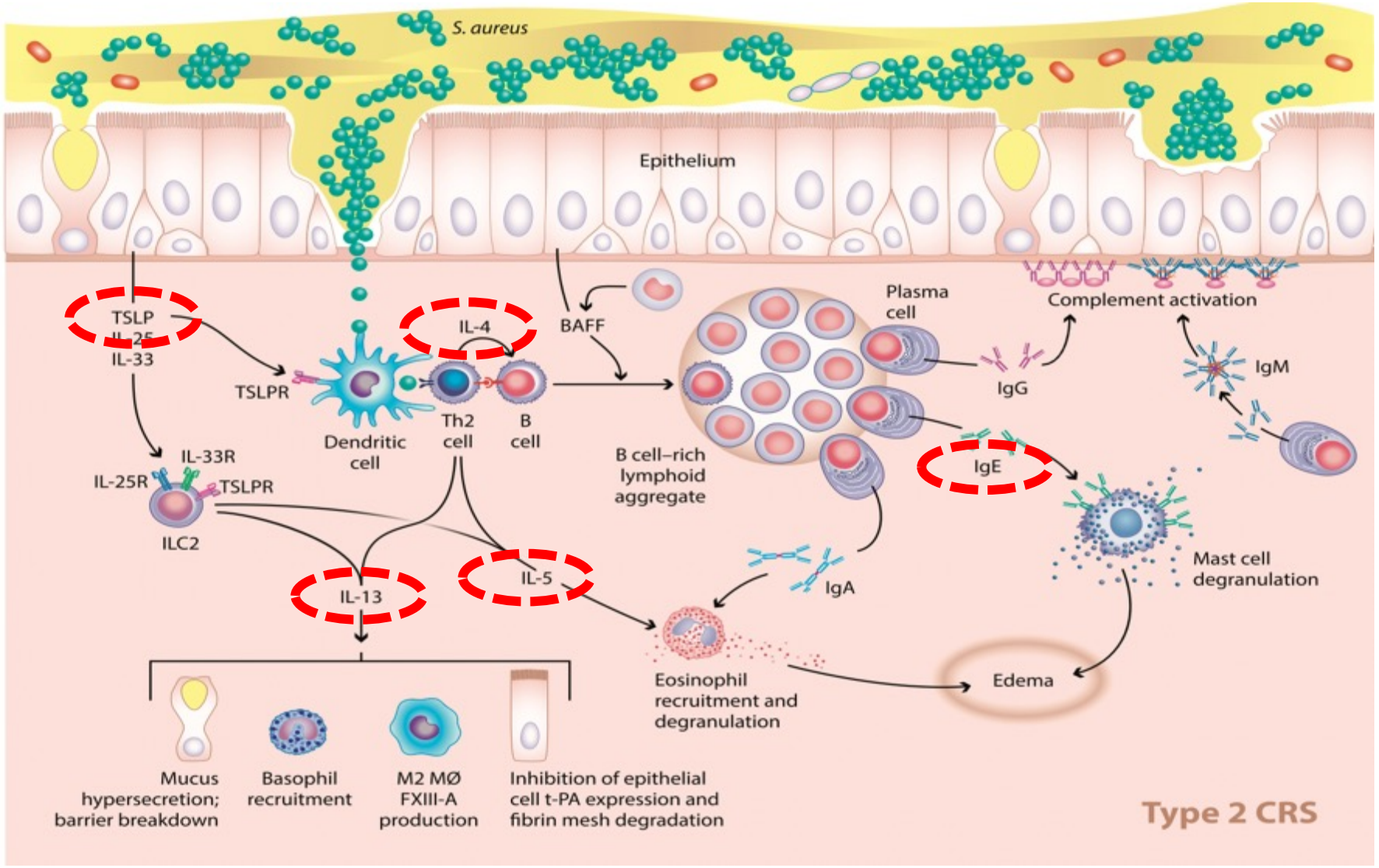
CRSwNP: Targeting Type 2 Inflammation Drivers



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What we know about CRSwNP ?

- Type 2 cytokines including IL-4, IL-5, and IL-13 as well as IgE are expressed in about 80% of CRSwNP mucosal tissue.
- The expression of type 2 cytokines is associated with asthma comorbidity and recurrence of disease after surgery and systemic steroids.
- Type 2 cytokines in CRSwNP are related to the inflammation found in most patients, with hypereosinophilia and IgE formation, and to the typical symptoms.

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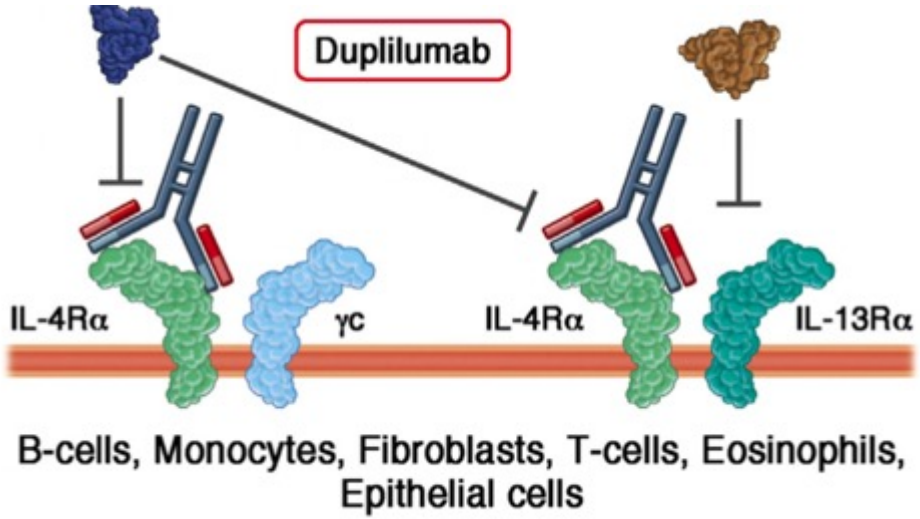
Dupilumab: FDA approved for CRSwNP in 2019

Approved August 12, 2020 In Canada



Claus Bachert, MD, PhD,a,b,c Nan Zhang, MD, PhD,a,b Carlo Cavaliere, MD,d Wen Weiping, MD,a Elien Gevaert, PhD,b and Olga Krysko, PhDb. Biologics for chronic rhinosinusitis with nasal polyps. Clinical reviews in allergy and immunology

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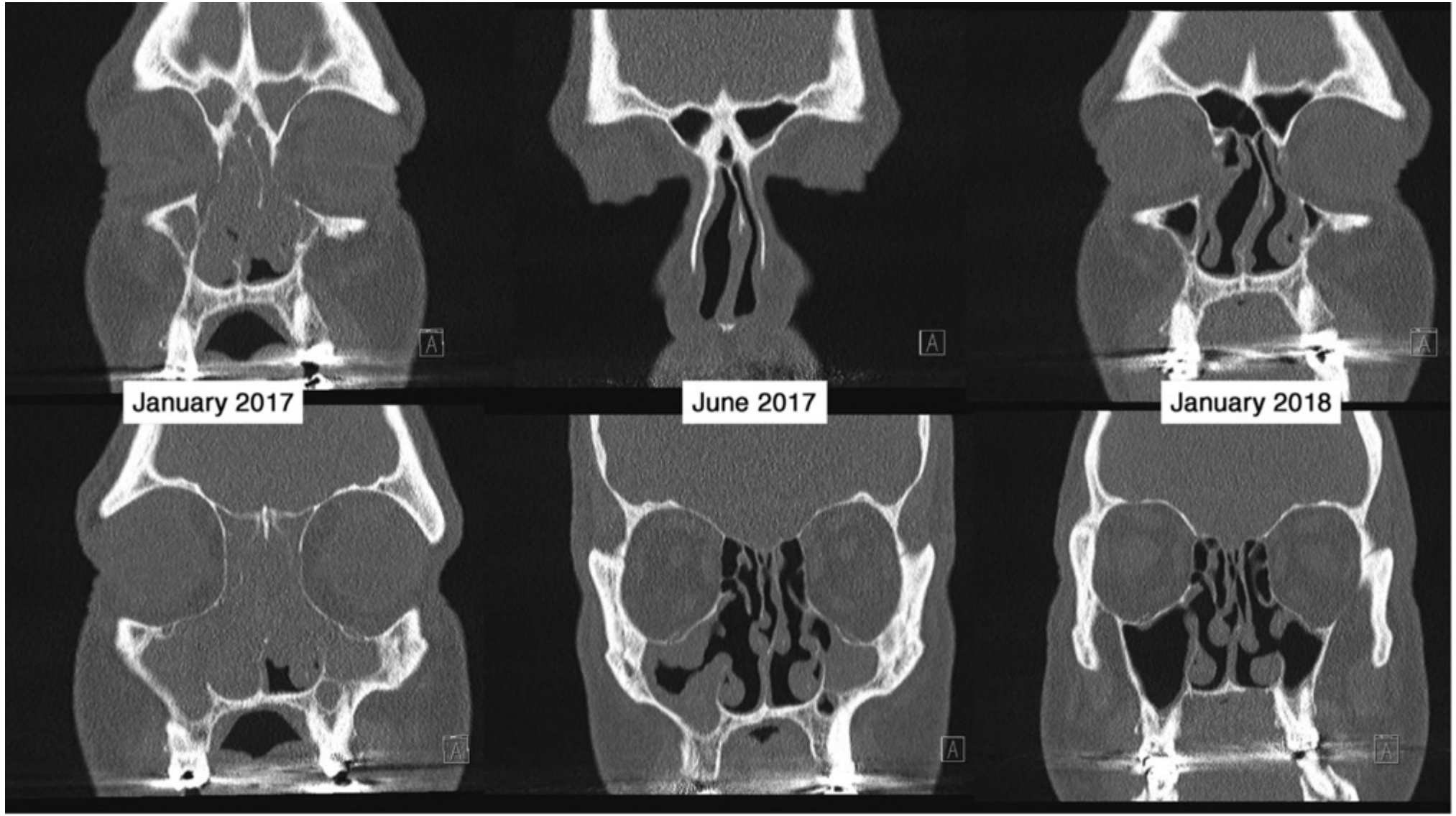

FIG 3. CT scans over 1 year in a patient with CRSwNP under dupilumab.

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Omalizumab: anti-IgE

Nasal Polyps: XOLAIR 75 to 600 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg).

<u>Approved July 19th, 2021 in Canada</u>

Table 3. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Adult Patients with Nasal Polyps

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Bodyweight							
		>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	> 125-150 kg
		Dose (mg)							
30 - 100	Every 4 Weeks	75	150	150	150	150	150	300	300
>100 - 200		150	300	300	300	300	300	450	600
>200 - 300		225	300	300	450	450	450	600	375
>300 - 400		300	450	450	450	600	600	450	525
>400 - 500		450	450	600	600	375	375	525	600
>500 - 600		450	600	600	375	450	450	600	
>600 - 700		450	600	375	450	450	525		
>700 - 800	Every 2 Weeks	300	375	450	450	525	600		
>800 - 900		300	375	450	525	600			
>900 - 1000		375	450	525	600				
>1000 - 1100		375	450	600					
>1100 - 1200		450	525	600	Insufficient Data to Recommend a Dose				
>1200 - 1300		450	525						
>1300 - 1500		525	600						

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

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Mepolizumab: anti-IL5

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Indirect comparison from phase 3

TABLE I. Phase 3 trials comparing type 2 biologics versus placebo where endoscopic NPS (0-8) was the coprimary end point and SNOT-22 (0-110) was a secondary outcome

Trial	SYNAPSE	POLYP 1	POLYP 2	SINUS 24	SINUS 52
Drug	Mepolizumab	Omalizumab	Omalizumab	Dupilumab	Dupilumab
Baseline NPS	5.5	6.25	6.25	5.94	6.09
Delta NPS	−0.8	−1.14	−0.59	−2.06	−1.80
% change	15	18	9	35	30
Baseline SNOT-22	64	60	60	49	51
Delta SNOT-22	−13.7	−16.1	−15.0	−21.1	−17.4
% change	21	27	25	43	34

Brian J. Lipworth, MD, and Rory Chan, MBChB. The Choice of Biologics in Patients with Severe Chronic Rhinosinusitis with Nasal Polyps. J ALLERGY CLIN IMMUNOL PRACT DECEMBER 2021

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Cochrane Review of The Effects of Biologics For The Treatment of CRSwNP[1]

Summary of findings of selected biologics for the treatment of CRSwNP

	Dupilumab	Omalizumab	Mepolizumab
Disease severity	**High-certainty evidence** for large reduction in the extend of the disease as measured by CT scan **Moderate-certainty evidence** for large improvement in symptoms, increased generic HRQL, and large reduction in NPS	**Moderate-certainty evidence** for possible reduction in the extend of disease when assessed by NPS and very low-certainty when assessed with CT scans	**Very uncertain-evidence** for may improve NPS
Disease-specific and generic HRQL	**High-certainty evidence** for large improvement in disease-specific HRQL compared with placebo **Moderate-certainty evidence** for large improvement in increased generic HRQL	**Moderate-certainty evidence** for probable large improvement in disease-specific HRQL compared with placebo	**Low to very low certainty-evidence** for may improve both disease specific and generic HRQL
Need for surgery	Probably results in a large reduction but it is difficult to interpret the clinical implications of this finding because of methodological limitations	**Low-certainty evidence** for a possibly large reduction in the need for surgery	**Very uncertainty- evidence** for may reduce the need for surgery due to limitations of the methodology that limit the clinical interpretation of the data

CRSwNP= Chronic rhinosinusitis with nasal polyps; HRQL=health-related quality of life.

1. Chong LY, et al. *Cochrane Database Syst Rev*. 2021;3:CD013513.

Canadian Rhinology Working Group

CONSENSUS STATEMENT: BIOLOGIC THERAPIES FOR CHRONIC RHINOSINUSITIS (CRS)

INTRODUCTION

Biologics that target the Type-2 inflammatory pathway can improve recalcitrant signs and symptoms of CRS with nasal polyps

IL-4, IL-5, IL-13
IL-5R, IL-33,
IgE

METHODS

8 RCTs with 'Biologics' targeting Type-2 pathway

17 fellowship-trained rhinologists

28 Original Statements
11 Consensus Statements

RECOMMENDATIONS

Eligible Patients for Biologics

- ✗ Not for CRS without nasal polyps
- ✗ Not for recurrent sinusitis
- ✓ Use in CRS with nasal polyps
- ✓ Moderate-severe symptoms
- ✓ After FESS + appropriate medical tx
- ✓ Another Type 2 condition (ie.asthma) not required

RECOMMENDATIONS

Response to Therapy

- ✓ Optional CT scan to assess
- ✓ Response eval ≥16 weeks and 1 year
- ✓ Response = subjective + objective improvement
- ✓ Trial other biologics if failure
- ⚠ Biologics are safe

Management for CRS with nasal polyps should be case-based and may include Biologics in recalcitrant disease

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Key Messages

- CRS classification is based on anatomy, endotype and phenotype.
- CRSwNP is type 2 inflammation driven.
- Failure of initial medical management should be followed by referral to otolaryngologist for surgical assessment.
- Three biologics are FDA approved: Dupilumab (anti IL-4), Mepolizumab (anti-IL5), and Omalizumab (anti-IgE).
- Biologics are indicated in type 2 inflammation when appropriate medical and surgical treatment fails.

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