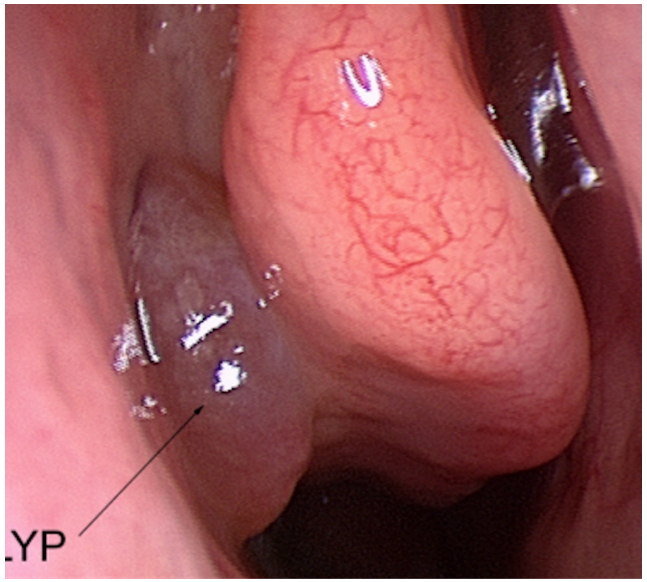
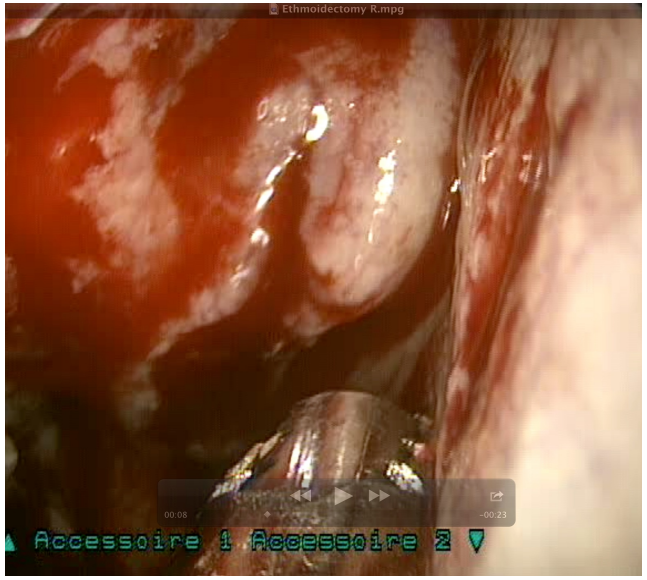
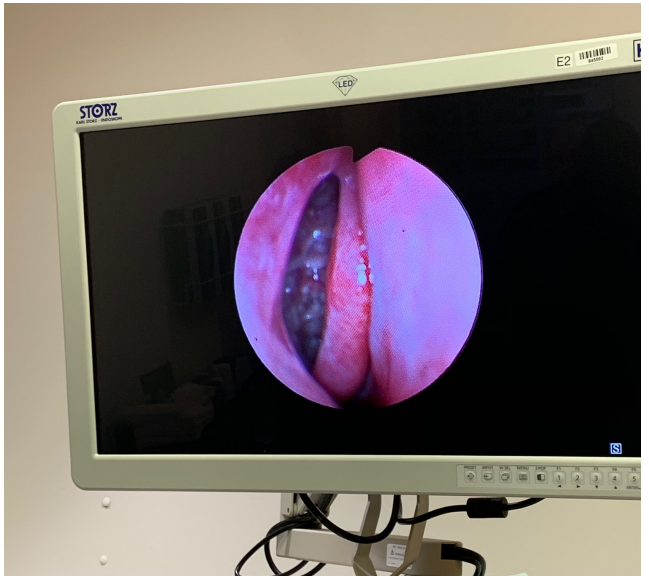


CRSwNP training session

Martin Desrosiers MD

OTL-HNS
Clinical Professor
Clinical researcher
Centre Hospitalier de l'Université de Montréal
Montréal, QC





Disclosures

Disclosures:

Martin Desrosiers, MD

Financial Interest/ Affiliation	Name of Company(s)
Grant/Research Support	Sanofi, Astra Zeneca, GSK
Employment/Honoraria/Consulting Fees/Travel expenses	Sanofi, Astra Zeneca, MEDA Pharmaceuticals
Major Stock Shareholder	Probionase Therapies Inc. (Topical nasal probiotics)
Membership on an advisory panel, standing committee, or board of directors	
Other Financial or Material Interest	President, Probionase Therapies
Other:	CPD designate, ORL-CCF Program, Université de Montréal

During the past 2 years, I **have/had** an affiliation (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of my presentation(s).

Definition: Chronic rhinosinusitis and nasal polyps[1–5]

Chronic Rhinosinusitis is a chronic inflammatory condition[1] of nose, paranasal sinuses and upper airways with persistent symptoms for ≥ 12 weeks[2,3]

EPOS 2020 defines **Chronic rhinosinusitis (with or without nasal polyps)** in adults as presence of ≥ 2 symptoms for ≥ 12 weeks3:

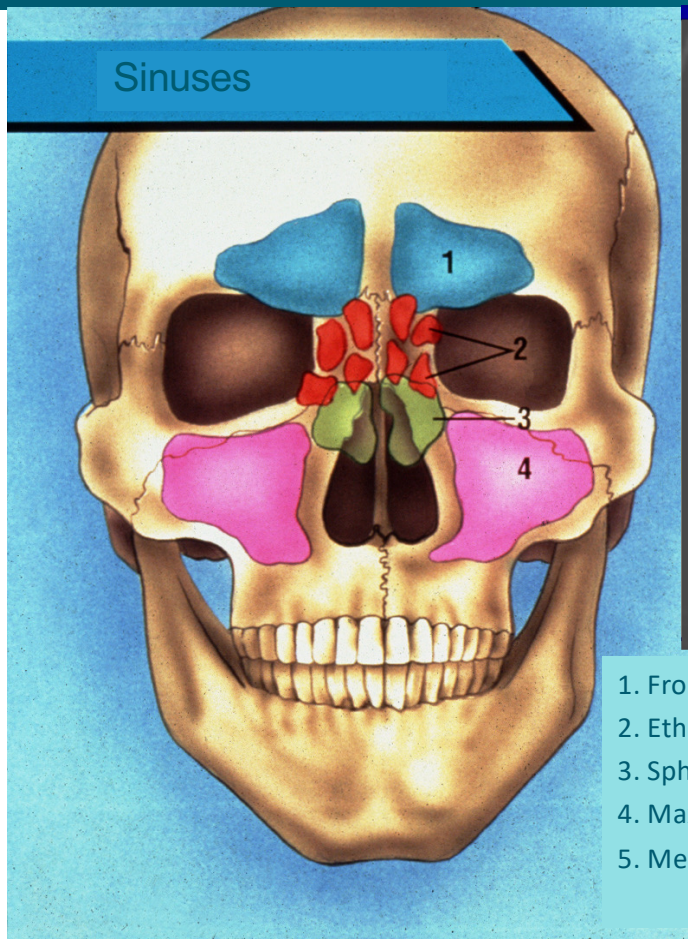
- Either nasal obstruction / congestion or nasal discharge (anterior / posterior nasal drip)
- Other symptoms could be:
  - facial pain / pressure
  - reduction or loss of smell

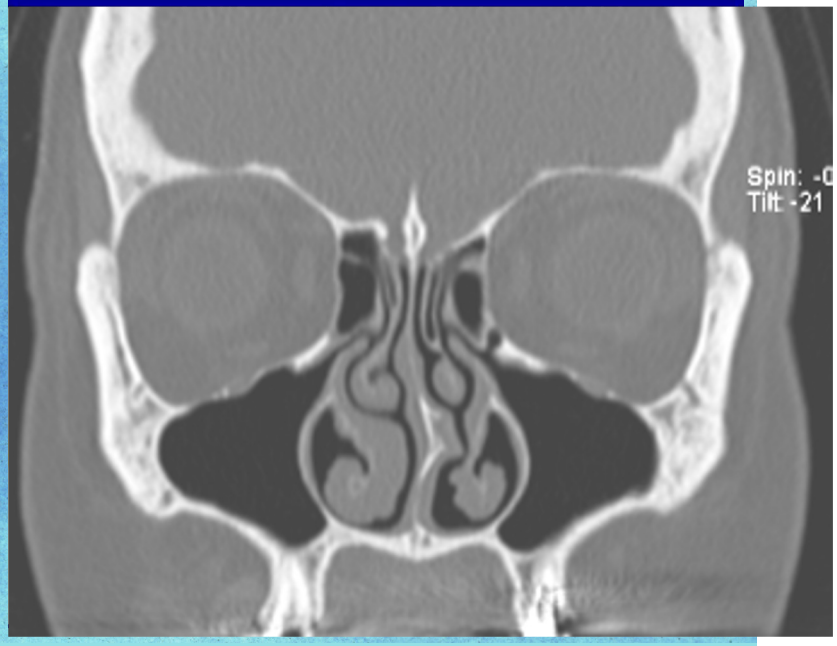
Nasal polyps constitute a **subtype of CRS**[4,5] and refers to the **benign inflammatory masses,** arising from the mucosa of the nose and paranasal sinuses[5]

CRS: chronic rhinosinusitis; EPOS: European position paper on rhinosinusitis and nasal polyps

1. Fokkens WJ et al. *Allergy*. 2019;74:2312–2319; 2. Schleimer RP. *Annu Rev Pathol*. 2017;12:331–357; 3. Fokkens WJ et al. *Rhinology*. 2020;58 (Suppl S29):1–464; 4. Bachert C et al. *World allergy Organ J*. 2014;7(1):25; 5. Hopkins C et al. *N Engl J Med.* 2019;381:55–63

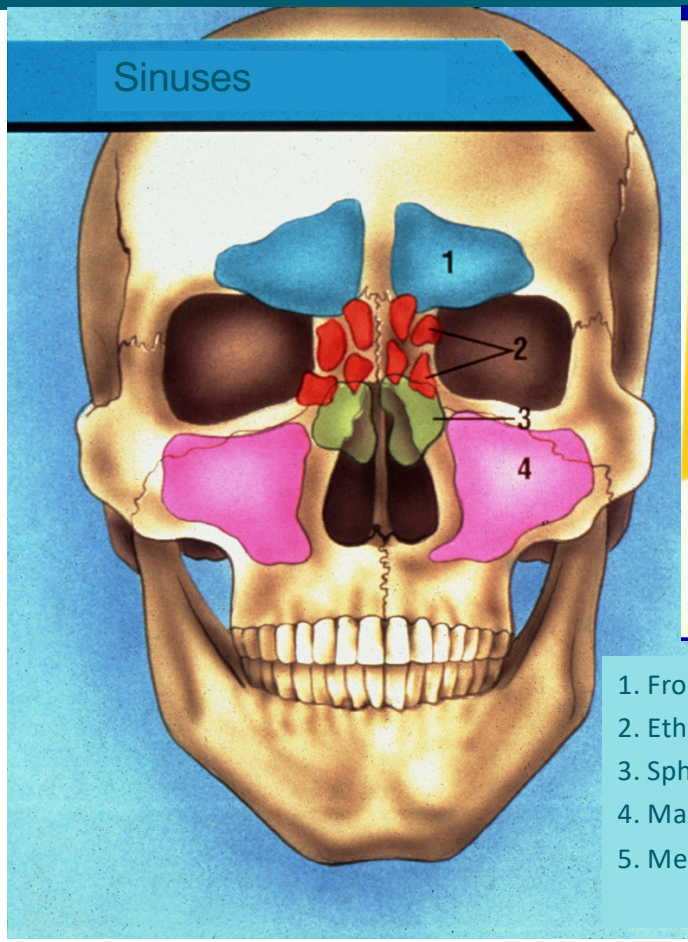
Anatomy and physiology

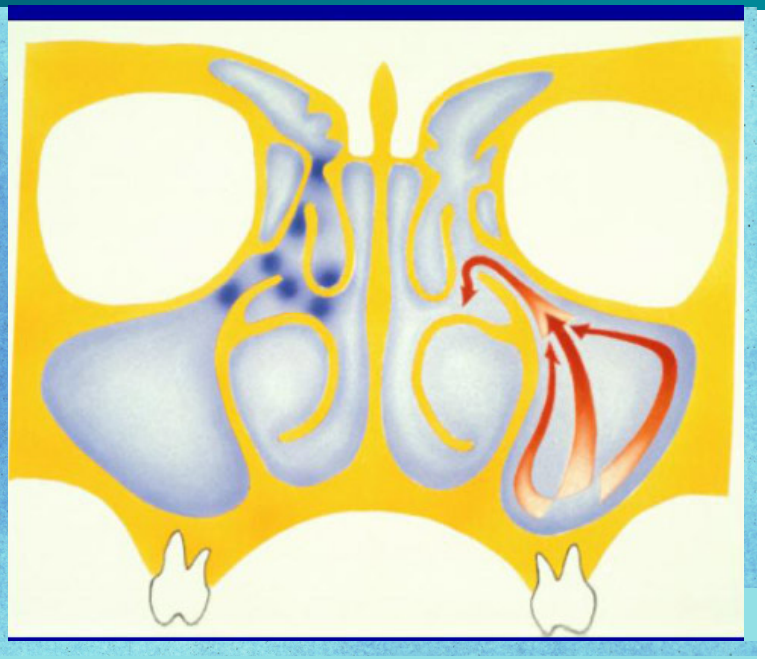




1. Frontal sinus
2. Ethmoid cells
3. Sphenoid sinus
4. Maxillary sinus
5. Meatus-orifice complex
6. Frontal recess
7. Ethmoid bulla
8. *Hamulus lacrimalis*
9. Ethmoid infundibulum
10. Maxillary sinus

Anatomy and physiology





1. Frontal sinus
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6. Frontal recess
7. Ethmoid bulla
8. *Hamulus lacrimalis*
9. Ethmoid infundibulum
10. Maxillary sinus

Diagnosis of CRS

Symptoms

- Nasal obstruction
- Facial pain / pressure
- Secretions: Anterior or posterior
- Recurrent infections
- Anosmia
- AND at least 1 objective finding
  - Endoscopy
  - Radiology

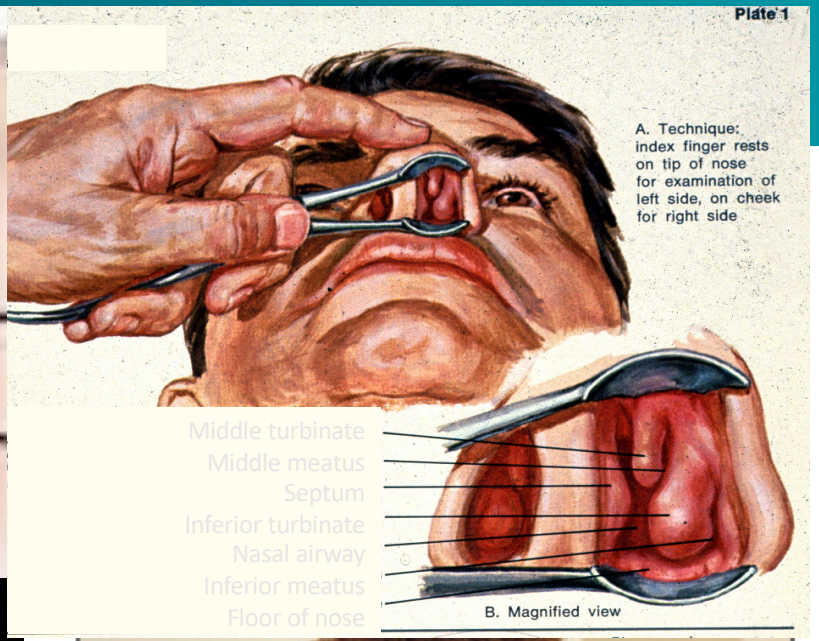
Desrosiers M, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *J Otolaryngol Head Neck Surg*. 2011 May;40(Suppl 2):S99-S193.

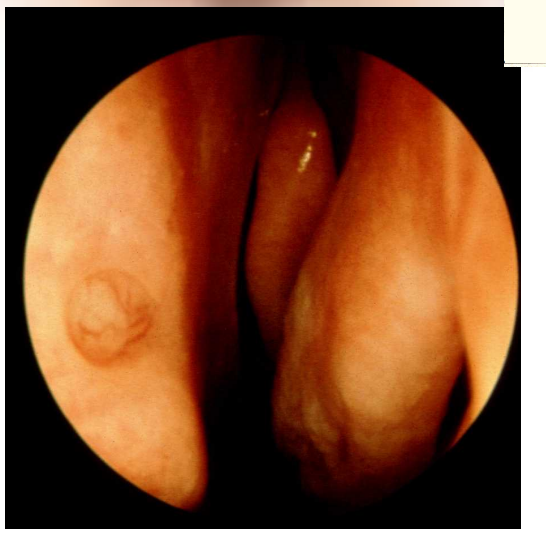
Nasal examination

Examiner et cherchez a identifier un site offensif

Décongestionner si possible

Otoscope peut remplacer lampe frontale



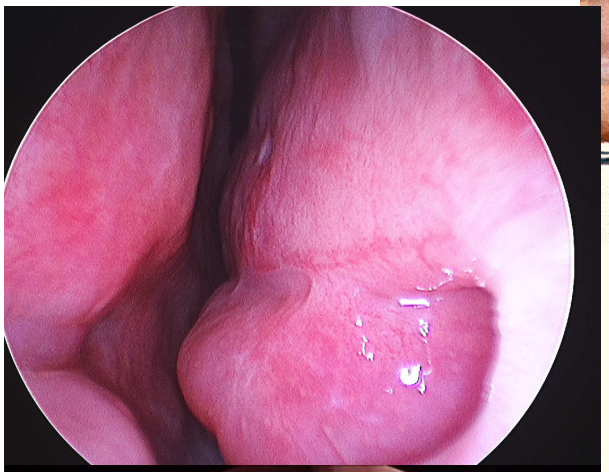


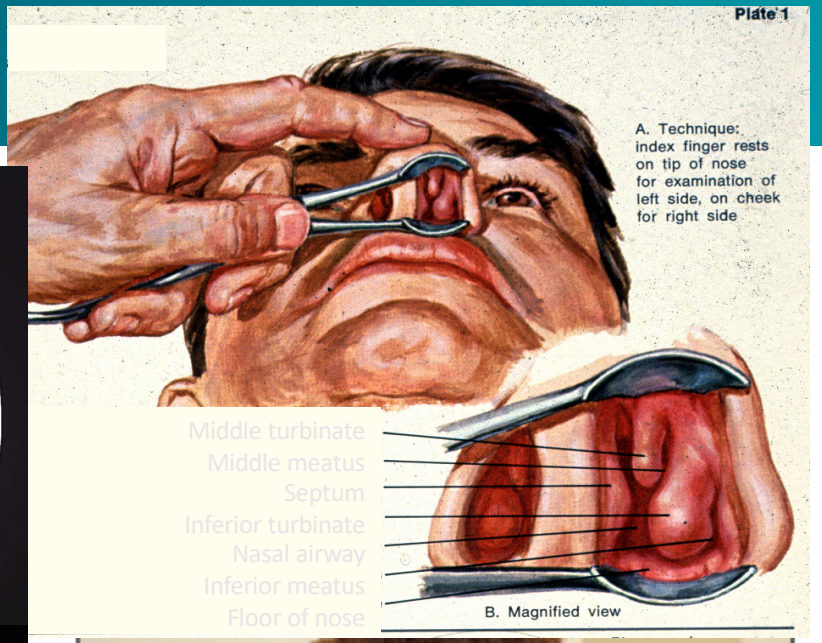
Si non sévère:

Examiner et cherchez a identifier un site offensif

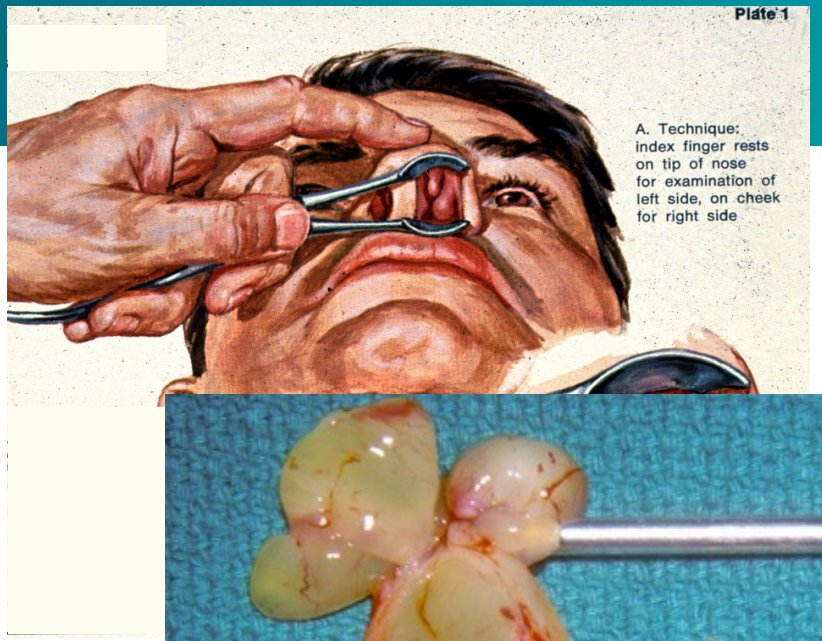
Décongestionner si possible

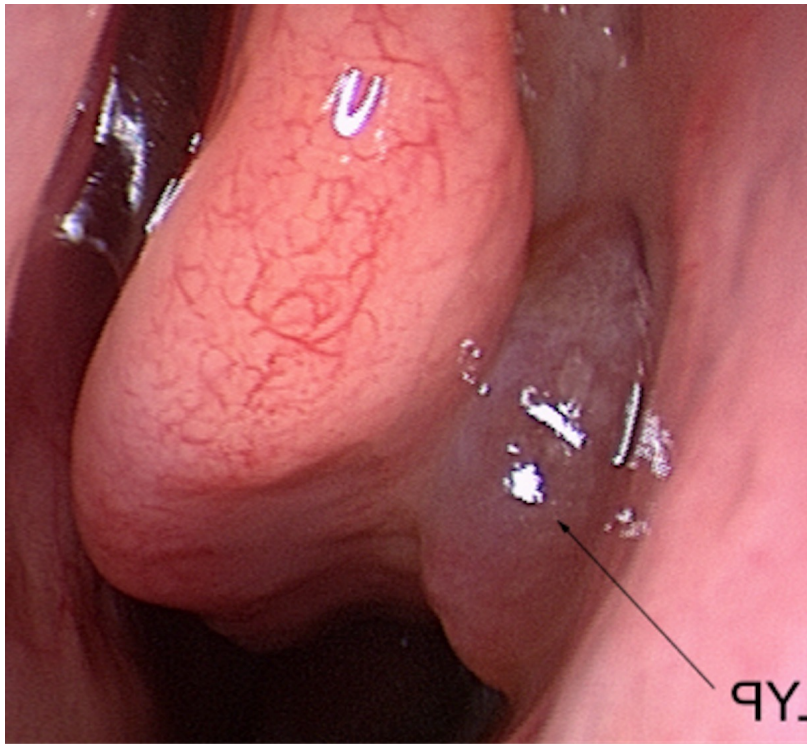
Otoscope peut remplacer lampe frontale



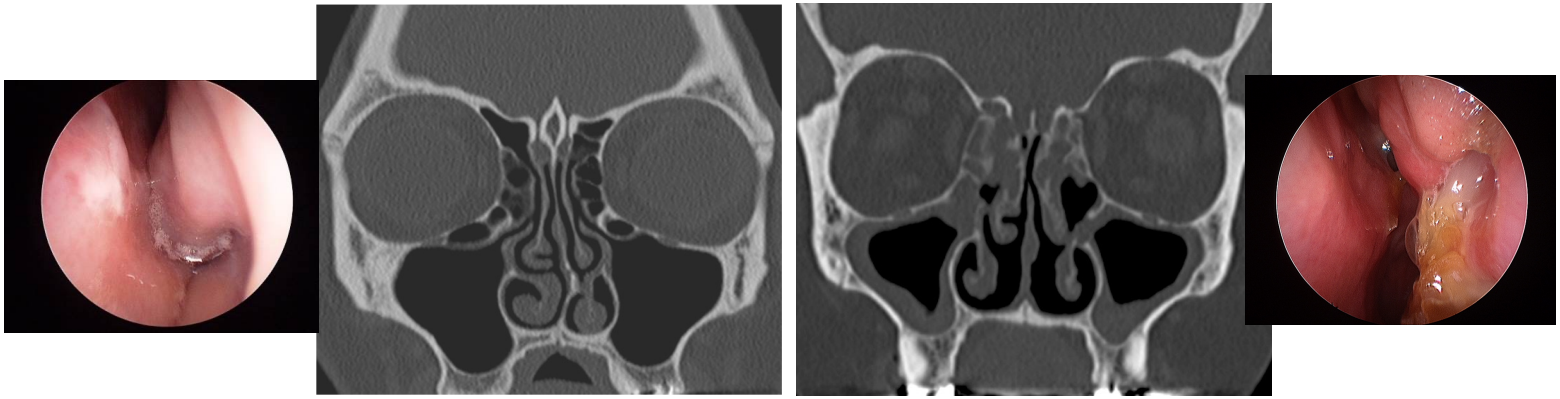


Nasal examination





Is It Rhinitis or Rhinosinusitis?



RHINITIS: Only nasal compartment is involved

SINUSITIS: Affects lining of sinuses as well

Swelling of sinus mucosa may protrude into nasal passages (nasal polyps)

Desrosiers M, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *J Otolaryngol Head Neck Surg*. 2011 May;40(Suppl 2):S99-S193.

CRS Subtypes

CRSwNP

Characterized by

- Mucopurlent drainage
- Nasal obstruction
- **Hyposmia**

Diagnosis requires

- At least 2 major symptoms
- Bilateral polyps in the middle meatus (on exam or endoscopy)
- Bilateral mucosal disease (CT scan)

CRSsNP

Characterized by

- Mucopurlent drainage
- Nasal obstruction
- Facial pain / pressure / fullness

Diagnosis requires

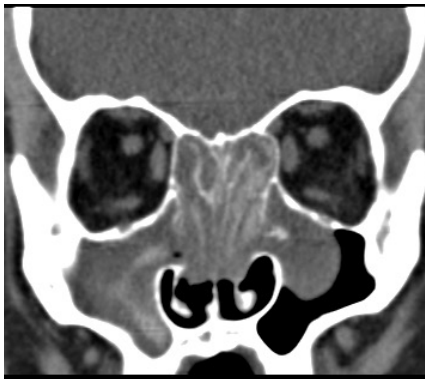
- At least 2 major symptoms
- Inflammation (endoscopy)
- Absence of polyps (endoscopy)
- Purulence from osteomeatal complex (endoscopy) or rhinosinusitis (CT)

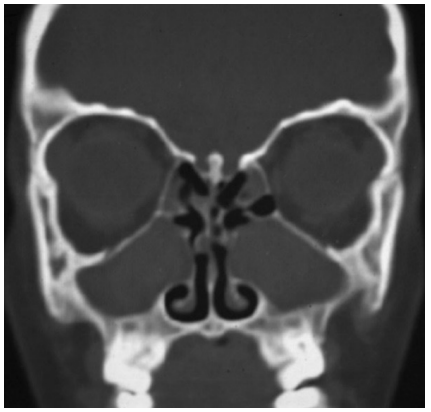
Radiologic Imaging

Seeks to identify patterns of disease not consistent with standard sinus disease

AFS appearance may be more difficult to treat

Beware of patients with maxillary-centric disease





International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol.* 2016 Feb;6(Suppl 1):S22-S209. doi: 10.1002/alr.21695.

Complications

CRS management strategies[1]

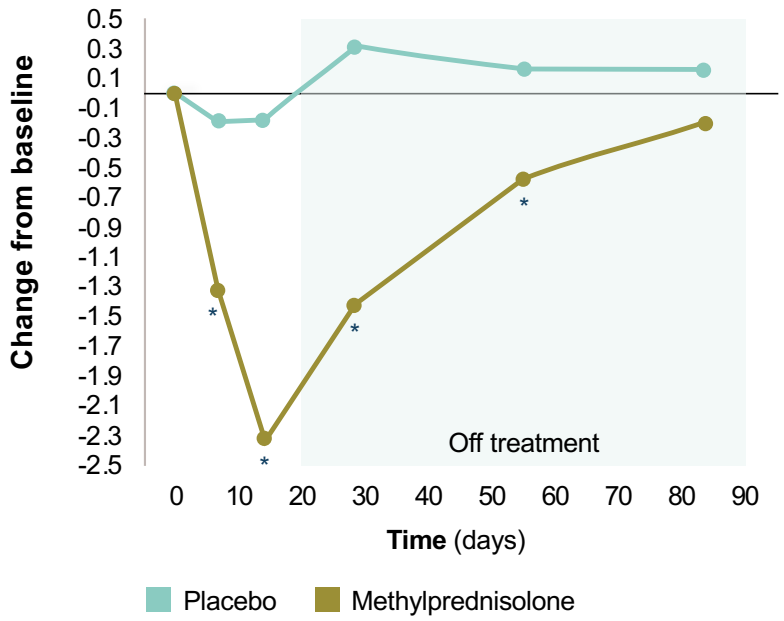
CRS therapy centers on corticosteroids and antibiotics

1. Desrosiers M, et al. *J Otolaryngol Head Neck Surg*. 2011 May;40(Suppl 2):S99-S193.

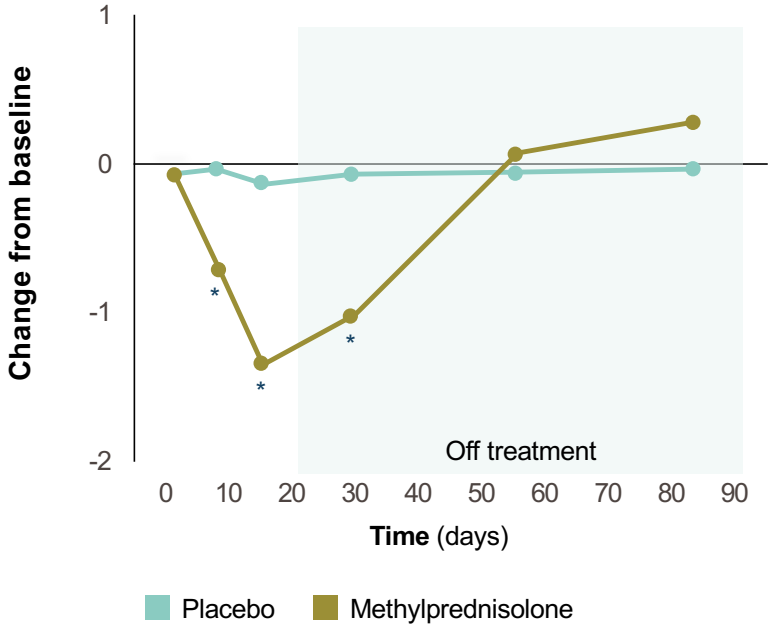
Systemic Corticosteroids Do Not Provide Long-Term Control

Patients with CRSwNP (n=47)

Nasal polyp score



Loss of sense of smell



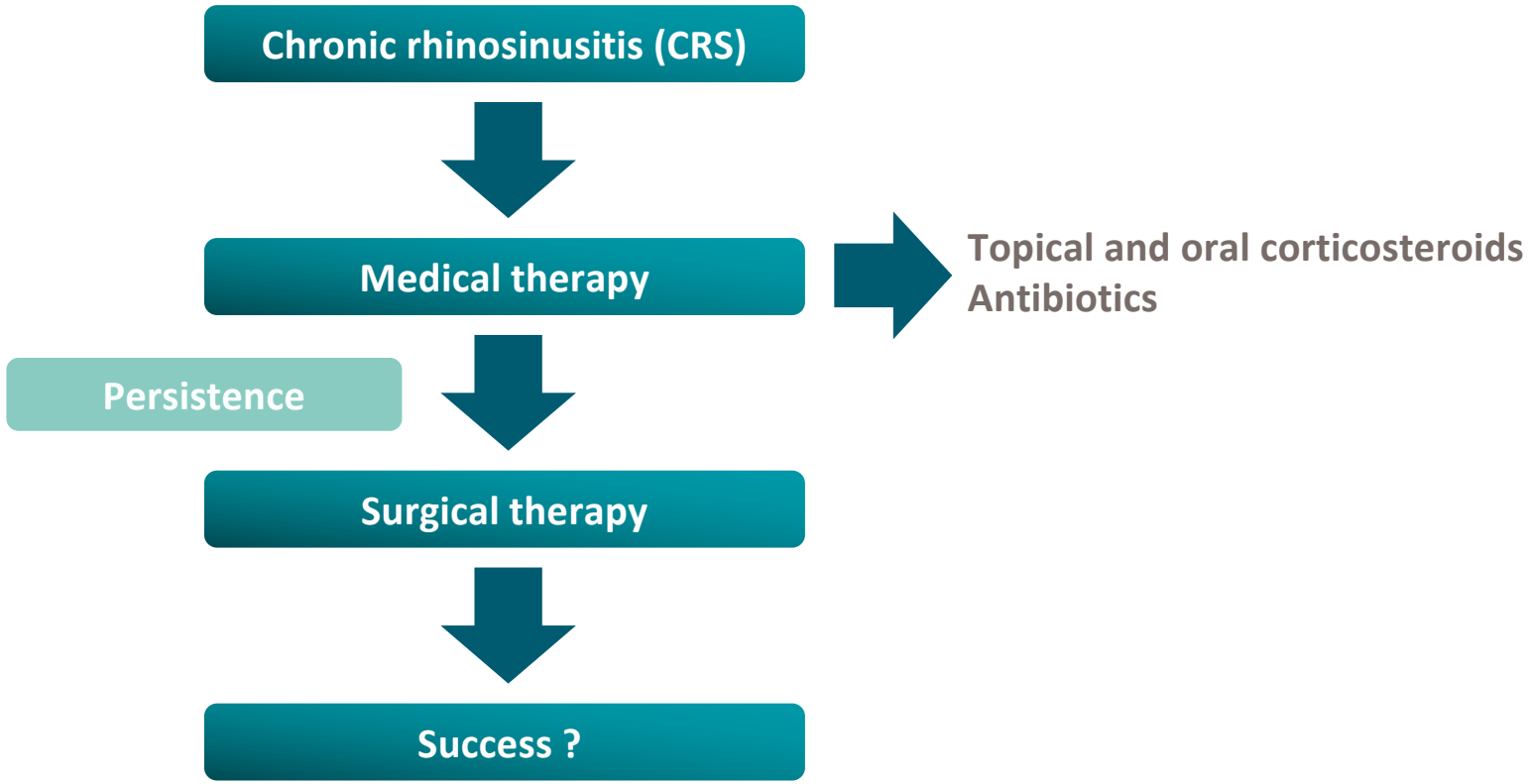
CRSwNP=chronic rhinosinusitis with nasal polyps.

*P<0.05, methylprednisolone versus placebo.

Van Zele T, et al. *J Allergy Clin Immunol*. 2010;125:1069-1076.e4.

CRS management strategies[1]

CRS therapy centers on corticosteroids and antibiotics



1. Desrosiers M, et al. *J Otolaryngol Head Neck Surg*. 2011 May;40(Suppl 2):S99-S193.

Surgery for chronic rhinosinusitis[1,2]

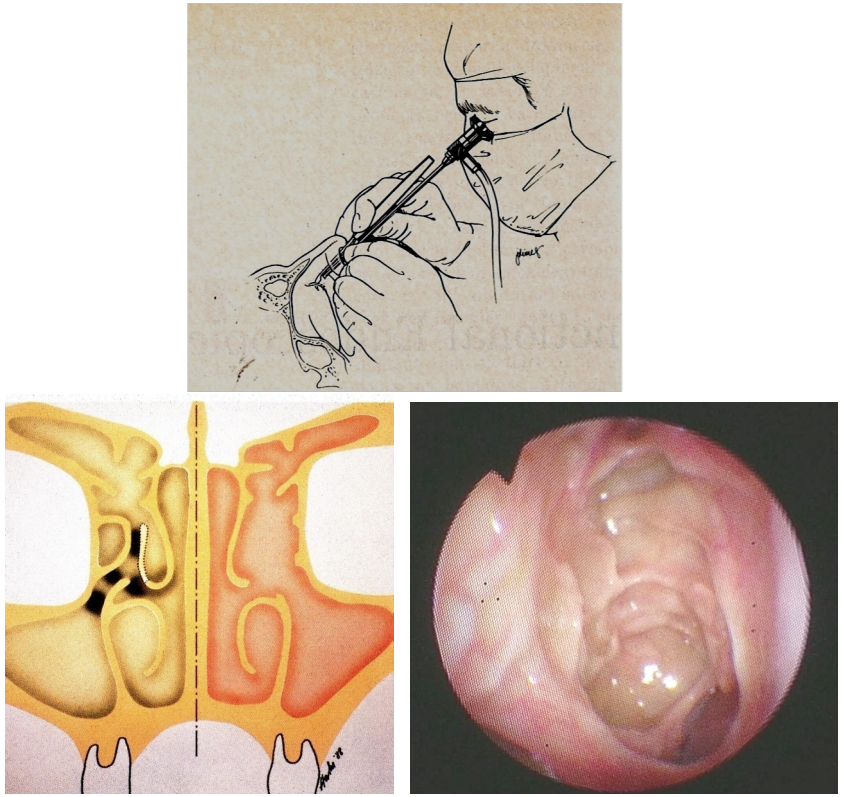
>500,000 sinus surgeries/year in US[1]

Goals of surgery[2]

- Improve nasal airflow and relieve sinus outflow obstruction
- Open sinuses for delivery of postoperative intranasal corticosteroids

When to consider surgery?[2]

- Surgery is indicated when symptoms persist despite appropriate medical therapy
- Minimum duration of medical therapy trial before considering surgery: 3–4 weeks



Images courtesy of M Desrosiers

1. Soler Amer J Rhinol. 2008
2. Orlandi RR, et al. Int Forum Allergy Rhinol. 2016;6 Suppl1:S22-209.

Objectives in managing CRSwNP with ESS: Canadian Experts Perspective

WHAT IS THE OPTIMAL OUTCOME AFTER ENDOSCOPIC SINUS SURGERY IN THE TREATMENT OF CHRONIC RHINOSINUSITIS?

A CONSULTATION OF CANADIAN EXPERTS

NT Saydy, SP Moubayed, M Bussières, A Janjua, S Kilty, F Lavigne, E Monteiro, S Nayan, M Piché, K Smith, D Sommer, L Sowerby, M Tewfik, IJ Witterick, E Wright, MY Desrosiers

INTRODUCTION

Optimal outcomes for endoscopic sinus surgery (ESS) in CRS are poorly defined in the literature

METHODS

- 12 subspecialty rhinologists
- Semi-structured interviews eliciting definition of operative success in CRS

RESULTS

Patient-reported treatment success = improvement in:

- chief complaint
- quality of life
- overall symptom control

RESULTS

Endoscopic evaluation of treatment success =

- adequate mucus outflow
- healthy mucosa
- patency of all explored cavities or ostia

ACCEPTABLE OUTCOME:

i) Subjective improvement of at least the minimal clinically improvement difference (MCID) of a validated patient reported outcome questionnaire, along with a satisfactory endoscopic result.

ii) Complete subjective resolution with a sub-optimal endoscopy.

Saydy et al. Journal of Otolaryngology - Head and Neck Surgery (2021) 50:36 https://doi.org/10.1186/s40463-021-00519-9

Objectives in managing CRSwNP with ESS: Canadian Experts Perspective

Validated Patient-Reported Outcome Measures Questionnaire	Nasal Endoscopy		
	Optimal	***Sub-Optimal***	***Bad***
Completely resolved	Optimal outcome	Acceptable success	Impending failure
Improved above MCID	Acceptable success	Acceptable success	Imminent failure
Minimal or no improvement	Consider other etiology for symptoms	Failure	Failure

MCID: Minimal Clinically Important Difference

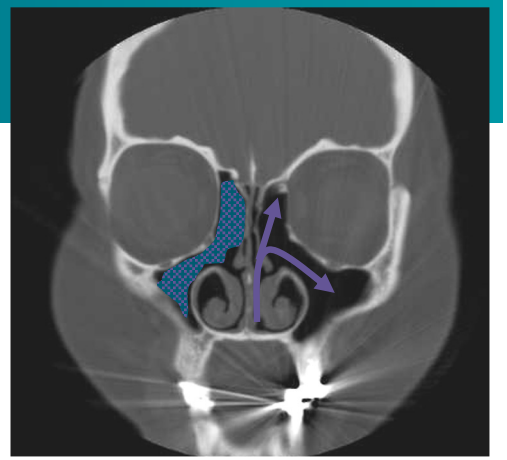
ACCEPTABLE OUTCOME:

i) Subjective improvement of at least the minimal clinically improvement difference (MCID) of a validated patient reported outcome questionnaire, along with a satisfactory endoscopic result.

ii) Complete subjective resolution with a sub-optimal endoscopy.

Saydy et al. Journal of Otolaryngology - Head and Neck Surgery (2021) 50:36 https://doi.org/10.1186/s40463-021-00519-9

Managing T2 inflammation
Intranasal Corticosteroids:



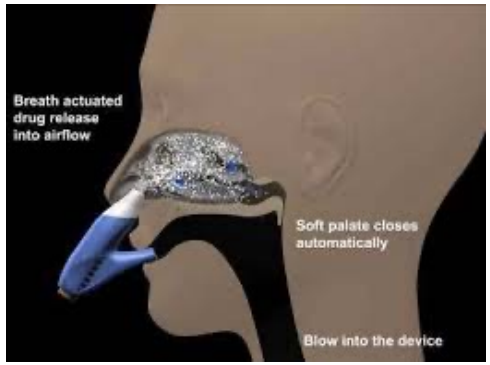
Safety profile is improved by **intranasal administration**

Sprays have limited distribution in the nose and may lack efficiency.

Can be improved by enhancing distribution

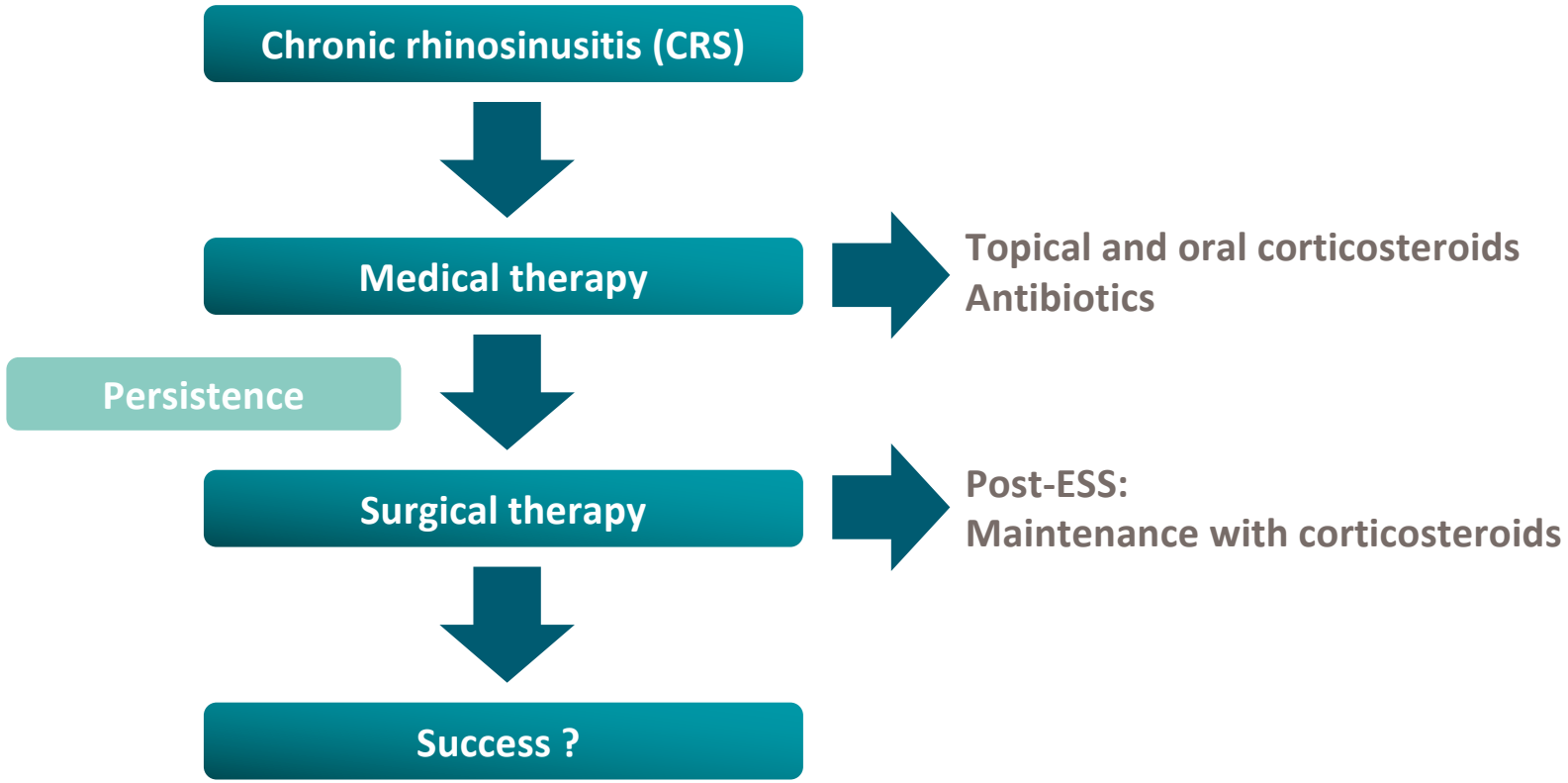
- Nasal washes; OptiNose (EXHANCE)

These remain of limited effectiveness in the patient with severe polyps or those already having failed these approaches.



CRS management strategies[1]

CRS therapy centers on corticosteroids and antibiotics

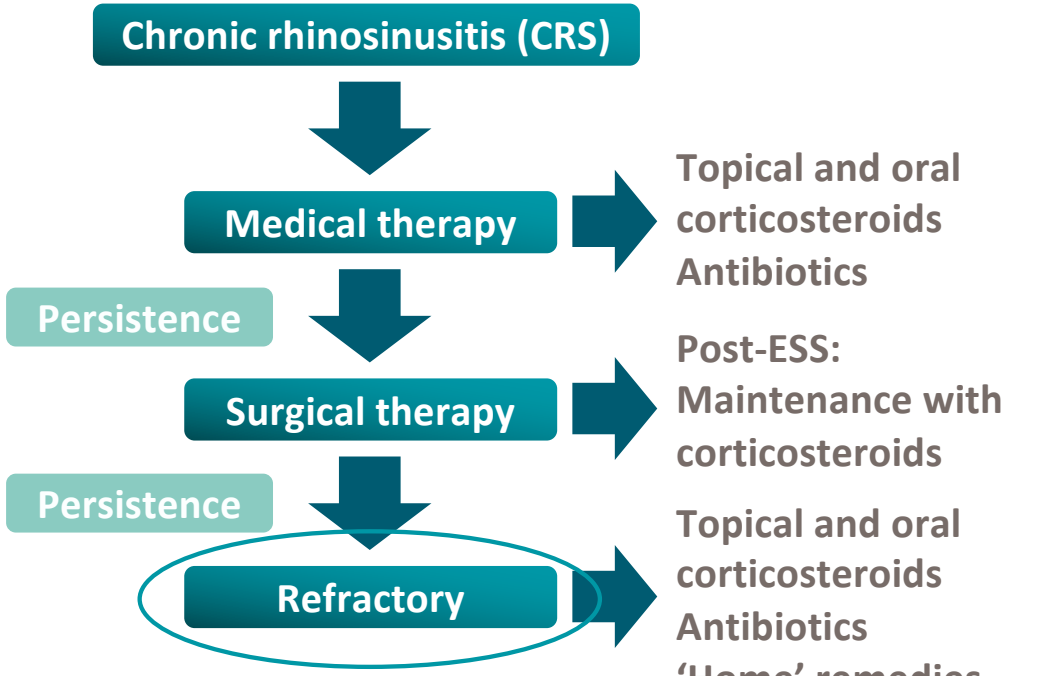


1. Desrosiers M, et al. *J Otolaryngol Head Neck Surg*. 2011 May;40(Suppl 2):S99-S193.

There is still room for improvement[1,2]

Polyp recurrence following ESS is common

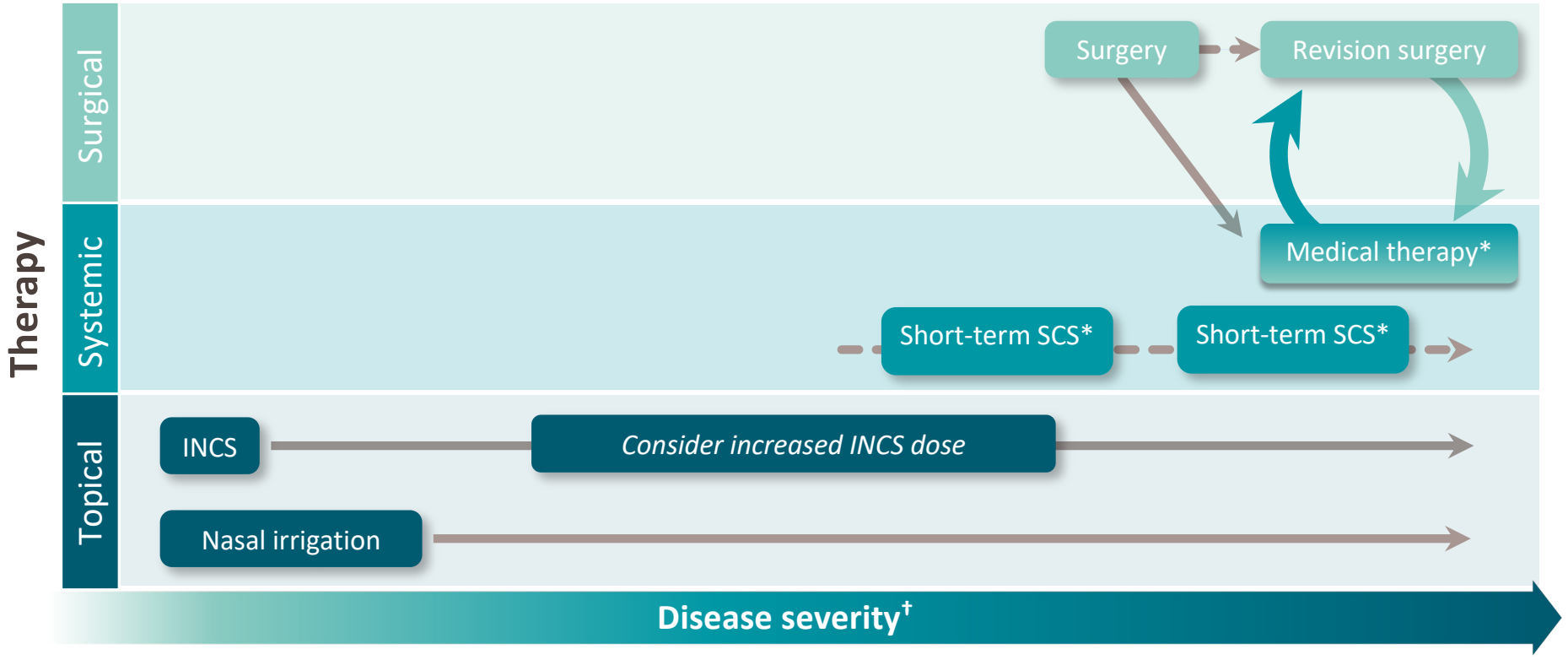
- 35% of patients have polyp recurrence by 6 months[1]
- 70% of patients have mucosal oedema by 6 months[1]
- Need for a second surgery within 5 years for 20% of patients who receive surgical treatment.[2]



Limited options available for the 'refractory' patient beyond surgery and prednisone

1.DeConde AS, et al. *Laryngoscope*, 2017; 127(3):550-555.
2.Hopkins, C, et al. *Laryngoscope*; 2009; 119(12): 2459-2465.

Severe disease leads to vicious cycle of treatment[1–3]



INCS=intranasal corticosteroid; SCS=systemic corticosteroid; VAS=visual analogue scale.

*INCS (consider increased dose), SCS, and/or nasal irrigation.[2] †Disease severity can be divided into mild, moderate, and severe based on total severity VAS score (1 to 10 cm).[1,2]

1. Fokkens WJ, et al. *Rhinology*. 2020;58(suppl S29):1-464. 2. Alobid I, et al. J Investig Allergol Clin Immunol. 2011;21(suppl 1):1-58. 3. DeConde AS, et al. *Laryngoscope*. 2017;127:550-555.

Etiology and pathogenesis of CRS[1–3]

CRS is a complex inflammatory disease with multifactorial etiology resulting from dysfunctional interaction between genetic, environmental factors and host immune system, contributing to its pathogenesis[1,2,3]

Genetic predisposition: CRS is estimated to exhibit heritability of 13-53% based on family studies, with highest heritability seen in Samter's triad. Asthma has an even higher heritability and is reported to occur in 20-31.9% of CRS subjects[1]

Fungus and bacteria: Pathogenic role for fungus and staphylococcus aureus as a trigger of CRS was proposed[2,3] though clinical studies cast significant doubt on role in etiology of CRS[3]

Microbial dysbiosis: The abnormalities and pathogenicity of collective microbial community in the nasal cavity may propagate sinonasal inflammation at anatomically vulnerable sites[2]

Epithelial Barrier and mucociliary dysfunction: CRS features dysfunctional sinonasal mucosa in which defects at epithelial surface, narrowing of sinuses[3] and mucociliary dysfunction may underlie its etiology[2]

CRS: chronic rhinosinusitis

1. Bachert C et al. World allergy Organ J. 2014;7(1):25; 2. Fokkens WJ et al. Rhinology. 2020;58(Suppl S29):1–464; 3. Orlandi RR et al. Int Forum Allergy Rhinol. 2016;6 Suppl 1:S22–209

What's wrong in CRSwNP

1) Mix of Type 2 and non-Type 2 Inflammation

2) Dysbiotic microbiome

3) Perturbed epithelial structure and function

Need to consider all three simultaneously

- Immune
- Microbiome
- Epithelial barrier

Isolated models (aka culture plate) may not reflect complexity of disease model

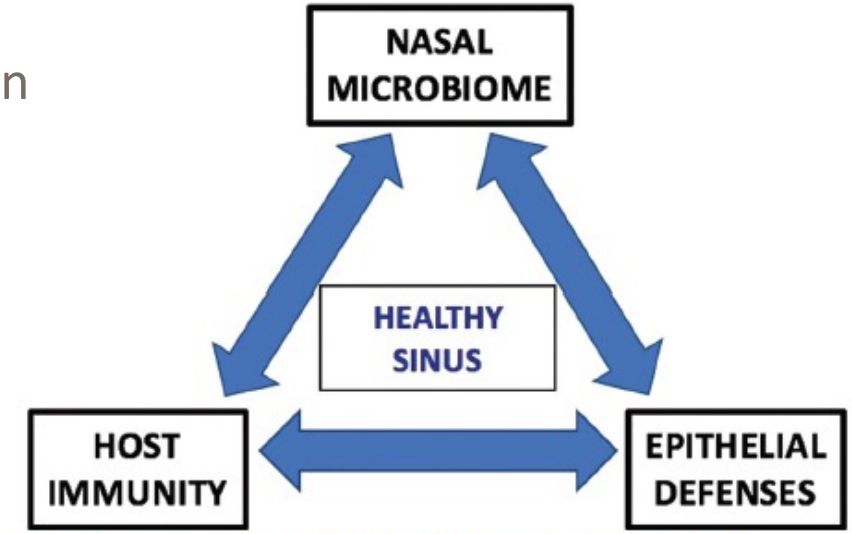
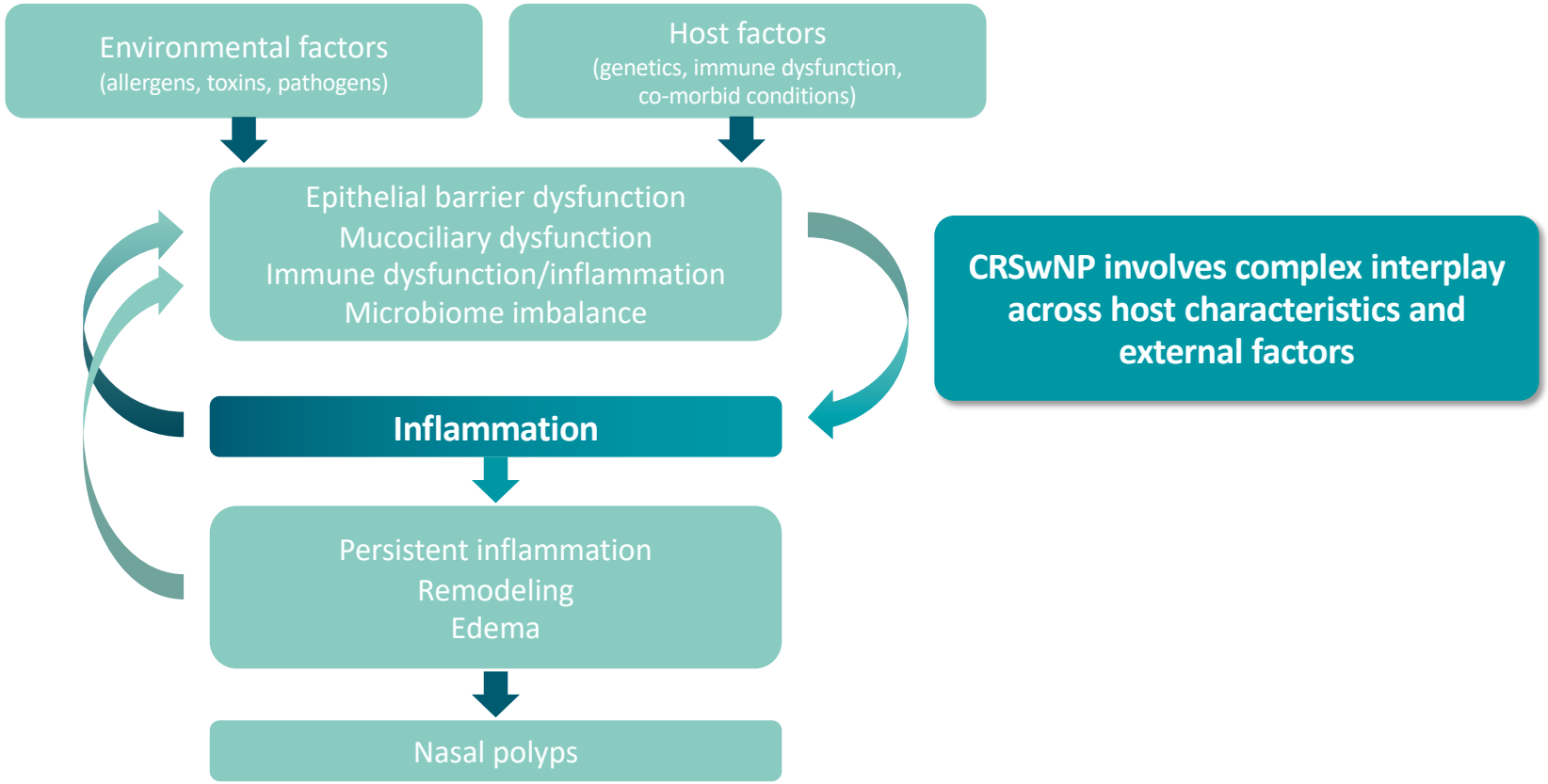


Figure 1. Major factors influencing chronic rhinosinusitis.

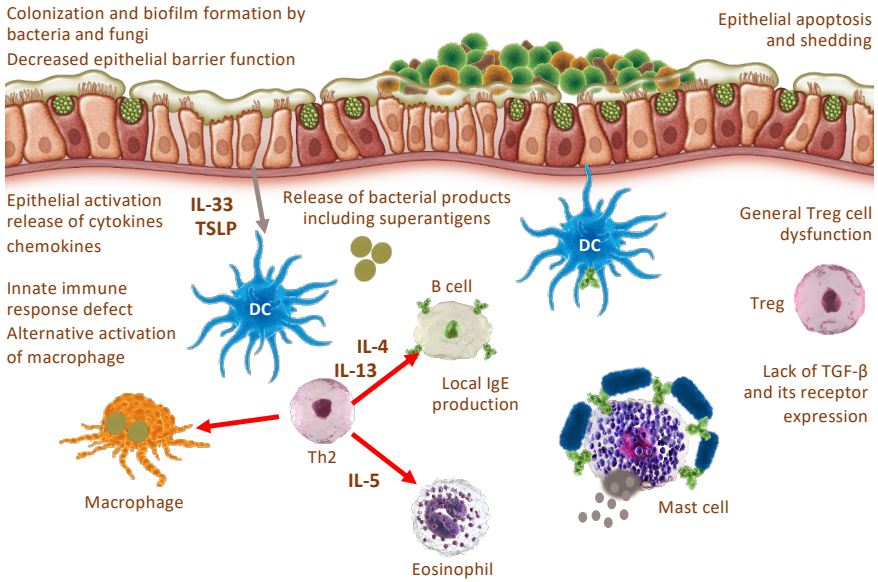
Inflammation is central to the multifactorial etiology of CRS[1–5]



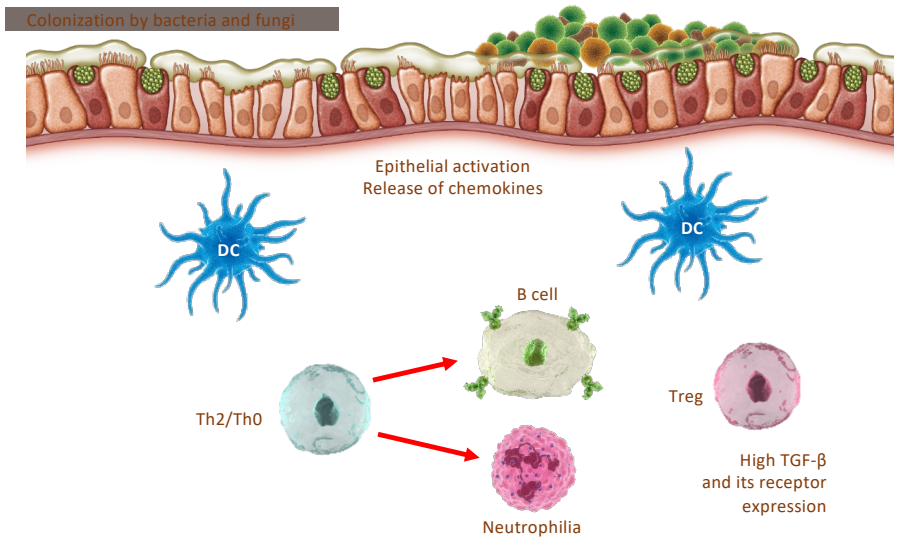
1. Fokkens WJ, et al. *Rhinol Suppl.* 2012;23:1–298;
2. Kim DW, et al. *Allergy Asthma Immunol Res.* 2017;9:299–306;
3. Schleimer RP, et al. *J Allergy Clin Immunol.* 2017;139:1752–1761;
4. Van Zele T, et al. *J Allergy Clin Immunol*. 2004;114:981–983;
5. Mahdavinia M, et al. *Clin Exp Allergy*. 2016;46:21–41

CRS is Frequently Associated with a Type 2 Inflammation

Type 2 inflammatory response



Non-Type 2 inflammatory response



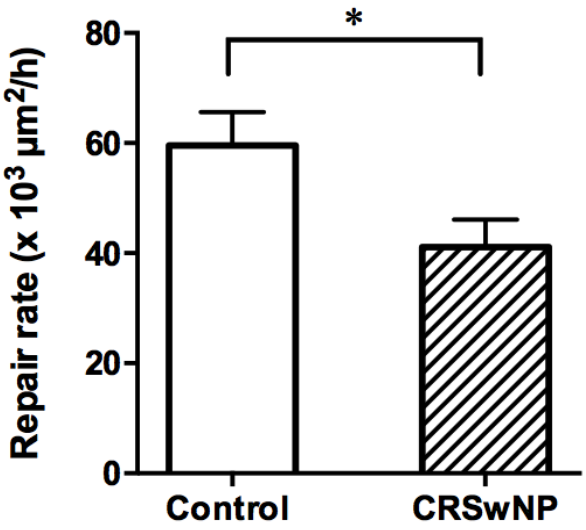
CRSwNP is associated with a Type 2 inflammatory signature in approximately 80% of cases[2-5]

DC, dendritic cell; IL, interleukin; TGF-β, transforming growth factor beta; Th, T helper; Th0, naïve T helper; Th1, Type 1 helper; Th2, Type 2 helper; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin

1. Bachert C, et al. *World Allergy Org J*. 2014;7:25;
2. Kim DW, et al. *Allergy Asthma Immunol Res*. 2017;9:299–306;
3. Wang X, et al. *J Allergy Clin Immunol*. 2016;138:1344–1353;
4. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35–50;
5. Shaw JL, et al. *Am J Respir Crit Care Med*. 2013;188:432–439

Epithelial repair is impaired in CRSwNP

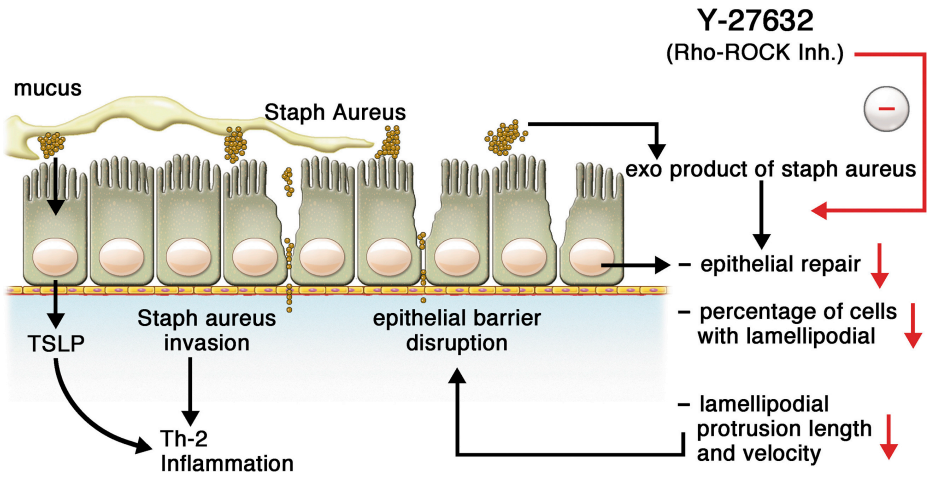
- CRS epithelium repairs poorly after injury
- S Aureus toxins aggravates this
- Worse in CRS PEC's



Editorial

***Staphylococcus aureus*, epithelial disruption, and nasal polyps: Are we one step ahead in combatting this foe?**

Mahboobeh Mahdavinia, MD, PhD,[a,c] and Pete S. Batra, MD, FACS[b,c] *Chicago, Ill*

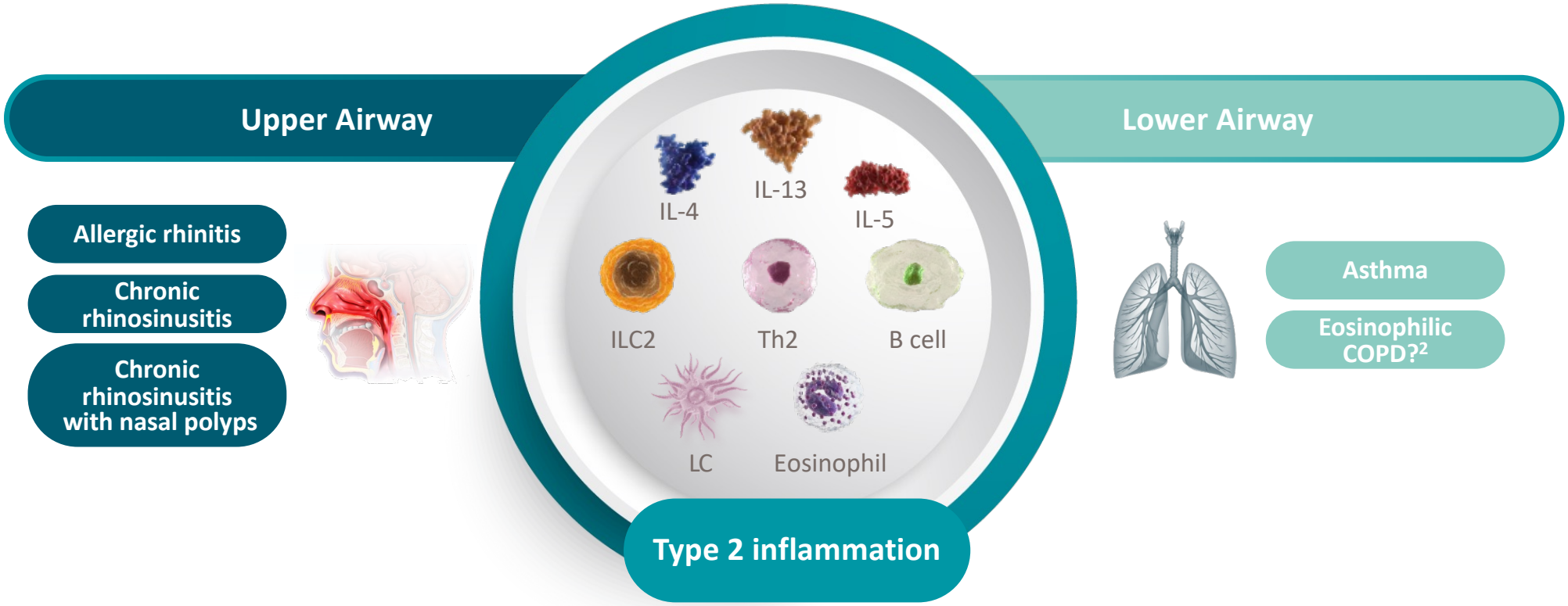


Decreased speed of wound closure indicates impaired epithelial regeneration

Primary sinonasal epithelial cells in ALI (*Air:Liquid Interface*)

Journal of Allergy and Clinical Immunology DOI: (10.1016/j.jaci.2018.11.021)

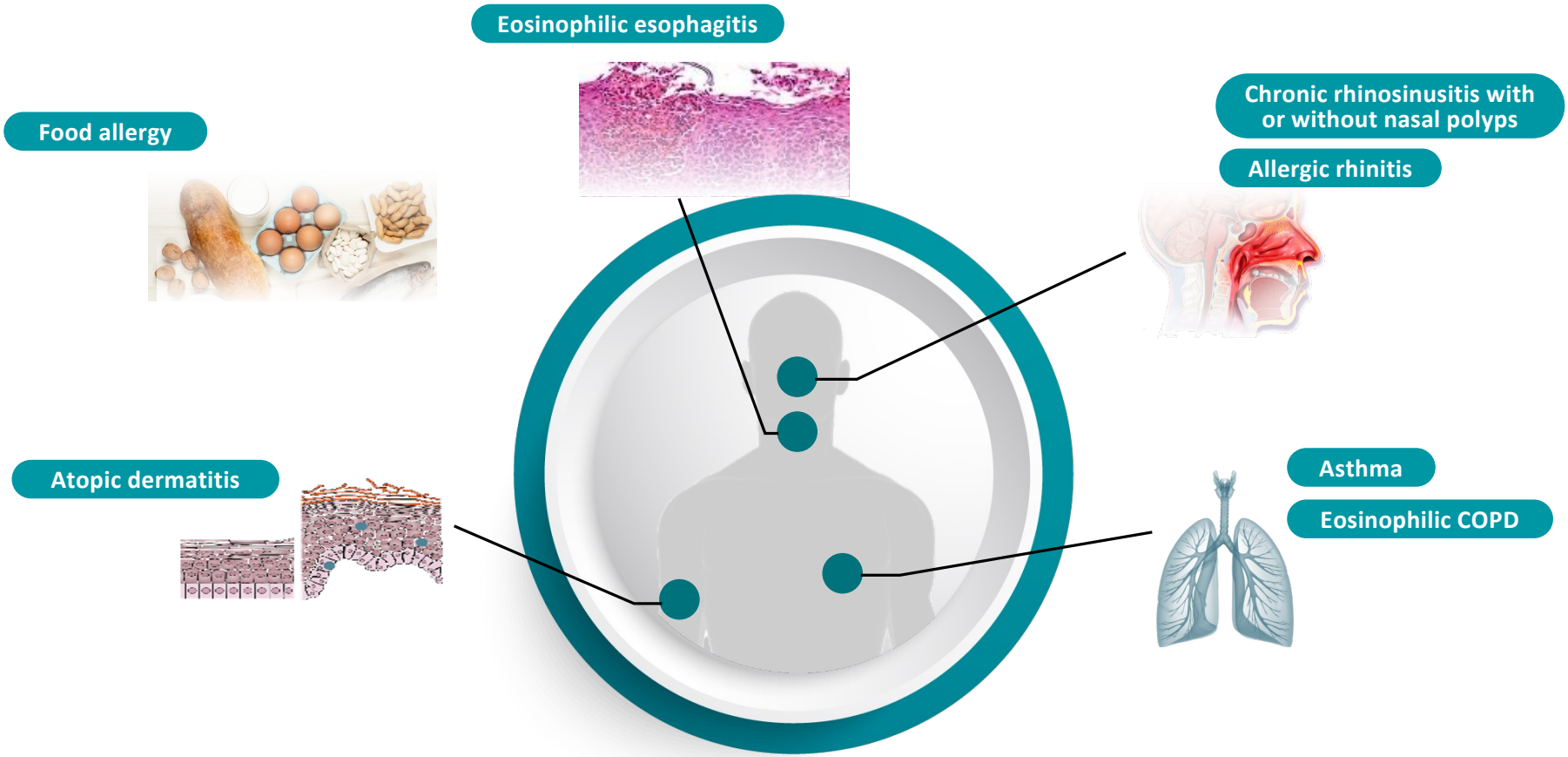
Chronic inflammatory airway diseases are frequently driven by type 2 inflammation[1,2]



COPD, chronic obstructive pulmonary disease; IL, interleukin; ILC2, type 2 innate lymphoid cell; LC, langerhans cell; Th2, type 2 helper

1. Gandhi NA, et al. *Nat Rev Drug Discov.* 2016;15:35–50; 2. Tworek D, Antczak A. *Adv Respir Med*. 2017;85:271–276

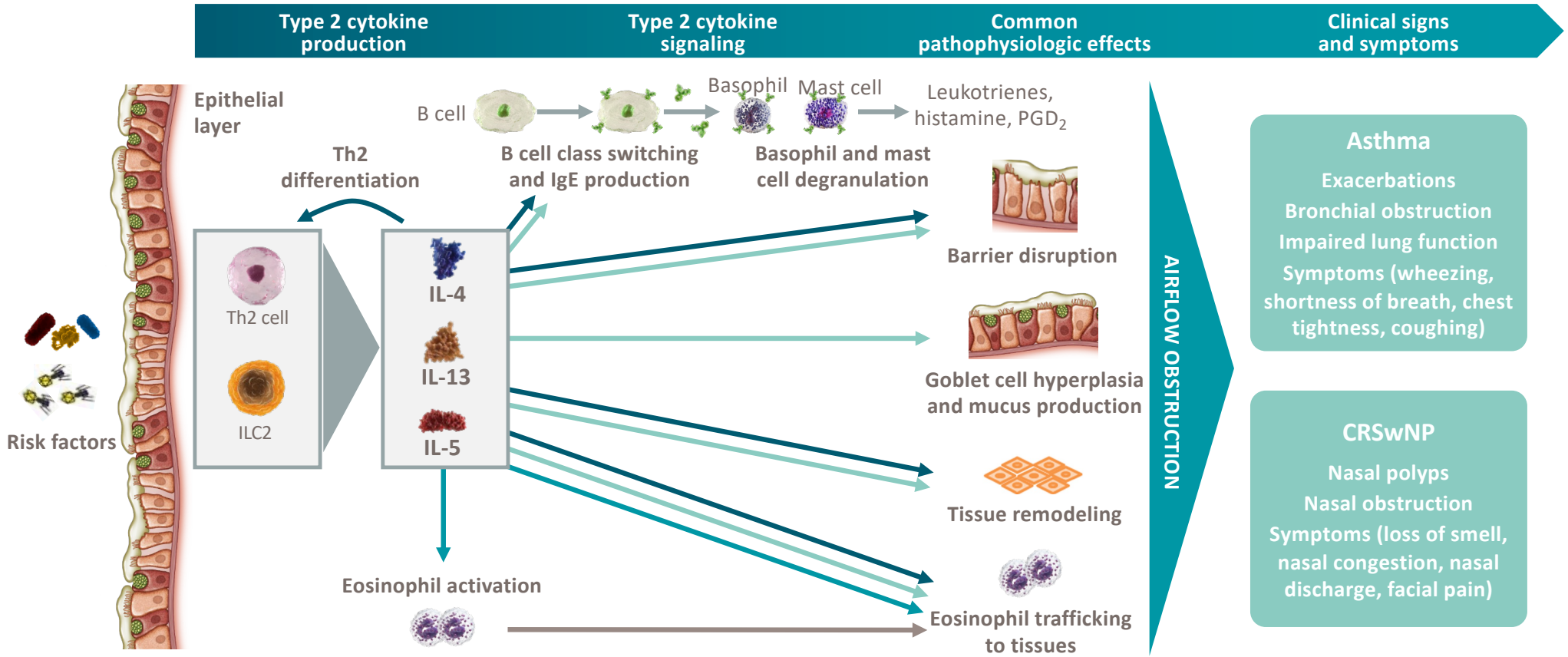
Type 2 inflammation underpins disease pathology across a range of organs[1–3]



COPD, chronic obstructive pulmonary disease

1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35–50; 2. Carr S, et al. *Allergy Asthma Clin Immunol*. 2011;7(Suppl. 1):S8;
3. Steinke JW, Wilson JM. *J Asthma Allergy*. 2016;9:37–43

The pathophysiologic features driven by IL-4 and IL-13 underpin the clinical manifestations of type 2 inflammatory airway diseases[1–4]



CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; ILC2, group 2 innate lymphoid cell; PGD2, prostaglandin D2; Th2, type 2 helper

1. Schleimer RP. *Annu Rev Pathol*. 2017;12:331–357; 2. Global Initiative for Asthma. GINA Report, Global Strategy for Asthma Management and Prevention. 2018. Available at https://ginasthma.org/gina-reports/. Accessed March 2019; 3. Israel E, et al. *N Engl J Med*. 2017;377:965–976; 4. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35–50

What would we like a Medication to do in CRS?

1) Control dysbiosis; restore healthy flora

2) Modulate Inflammation

3) Restore epithelium

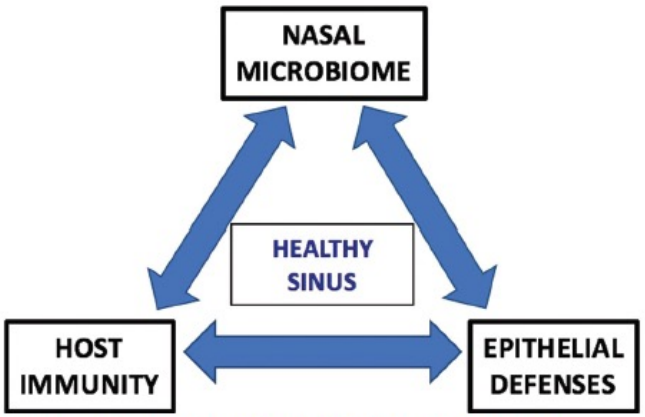


Figure 1. Major factors influencing chronic rhinosinusitis.

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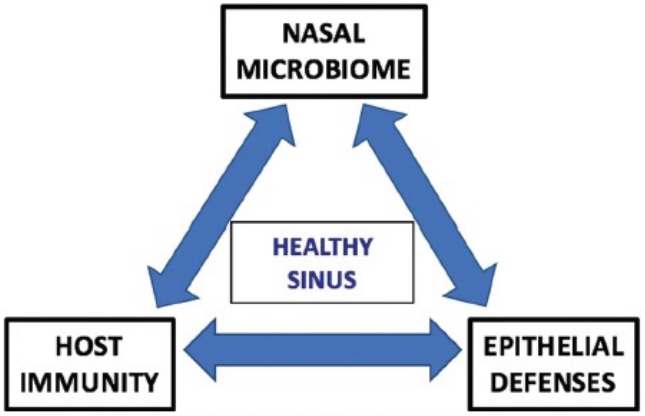


Figure 1. Major factors influencing chronic rhinosinusitis.

DUPIXENT®: Approved in Atopic Dermatitis

- **Approved March 28, 2017, for the treatment of adult patients with moderate-to-severe atopic dermatitis** whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

Baseline
- **IGA score: 4**
- **BSA affected: 86.5%**
- **EASI score: 51.5**
- **Pruritus NRS: 7**

Week 16
- **IGA score: 1**
- **BSA affected: 2.5%**
- **EASI score: 3.1**
- **Pruritus NRS: 1.6**

Example of a patient who achieved the primary end point. Photo used with permission.

Parameters measured in CRSwNP studies[1]

Co-primary endpoints

Change from baseline at Week 24 in nasal congestion and obstruction severity

Ranges from 0–3, is the monthly average of the daily morning AM patient-assessed daily symptom severity on the e-diary

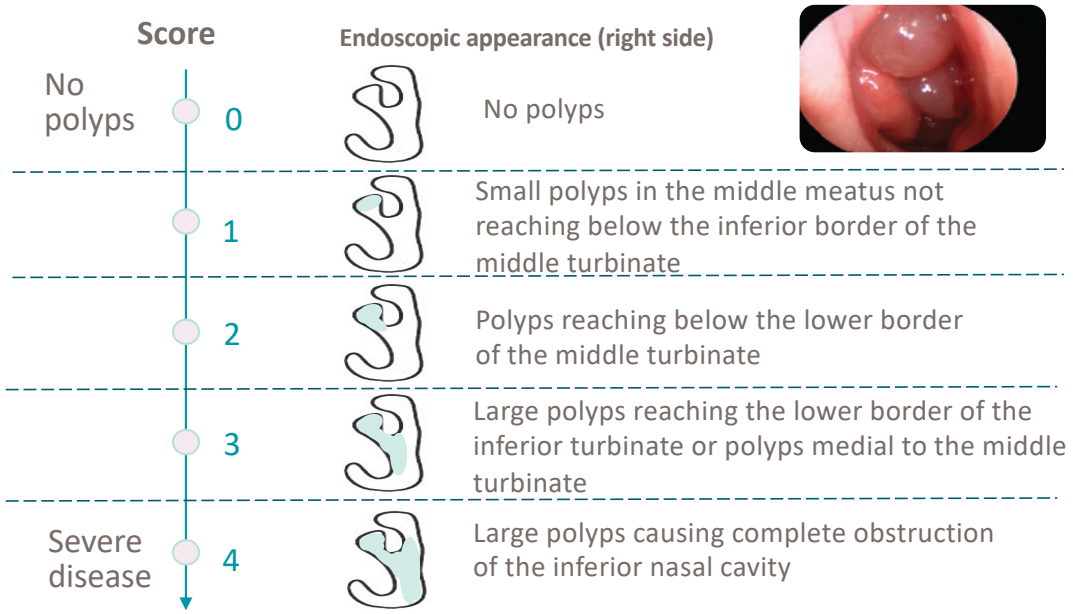
0=no symptoms,

1=mild symptoms,

2=moderate symptoms and

3=severe symptoms

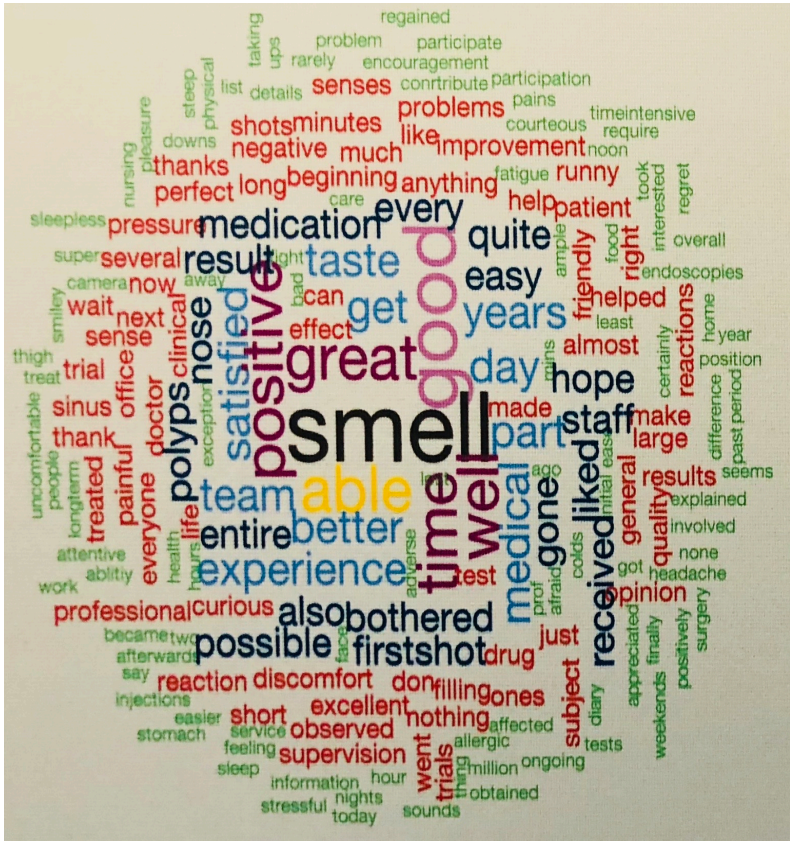
Change from baseline at Week 24 in endoscopic NPS



AM, ante meridiem; MFNS, mometasone furoate nasal spray; Q2W, every 2 weeks.

1. Bachert C, Lancet 2019; published online Sept 19. http://dx.doi.org/10.1016/S0140-6736(19)31881-1.

Never underestimate the importance of sense of smell for the patient…



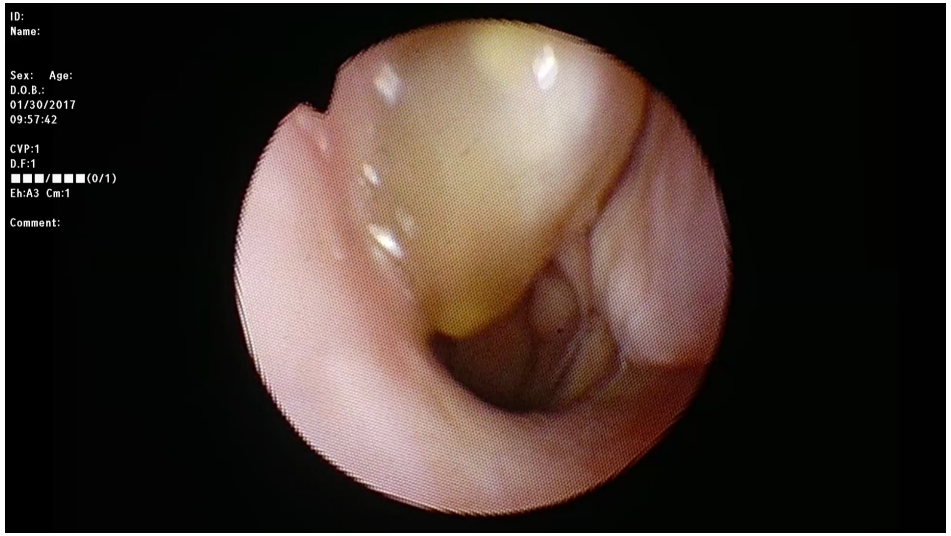
OMG OMG OMG

I CAN SMELL!!!! 🥳 🎈 🎉

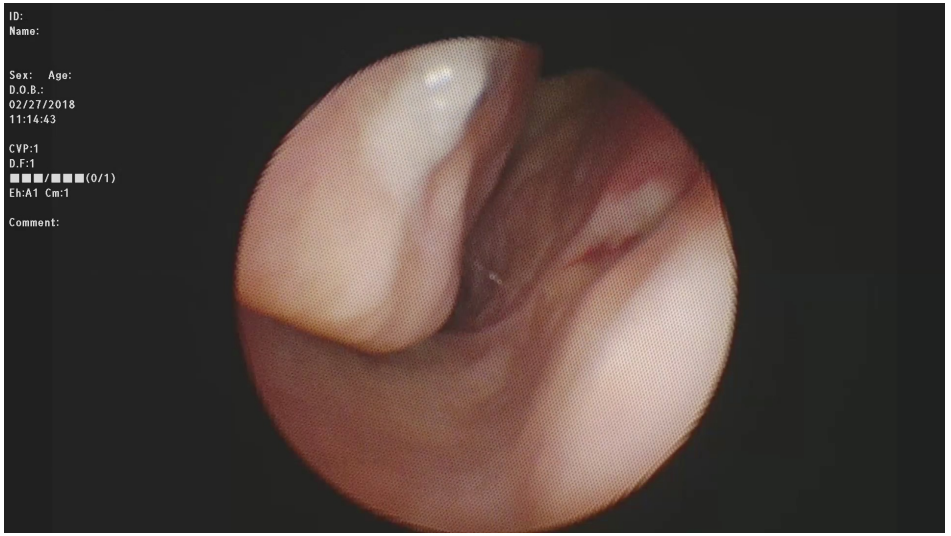
3 weeks post op today. I have the flu and my asthma has been triggered bad so I am back on steroids which I think has cleared up the remainin… See More

Example of T2 biologic effect on CRSwNP

Pre-Study



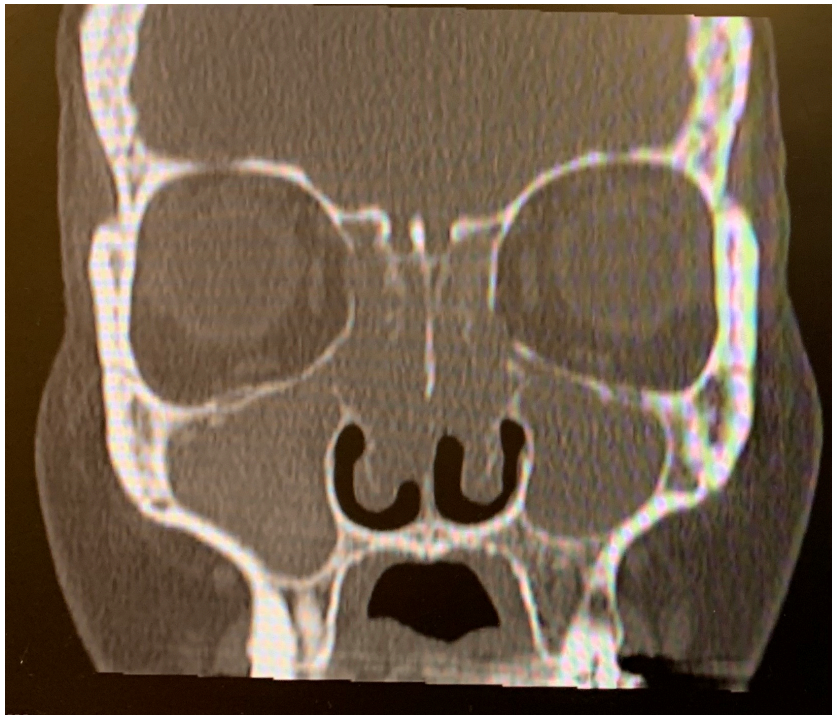
After 10 injections



Credit: Martin Desrosiers MD, Montréal, QC, 2018

Example of T2 biologic effect on CRSwNP

Pre-Study



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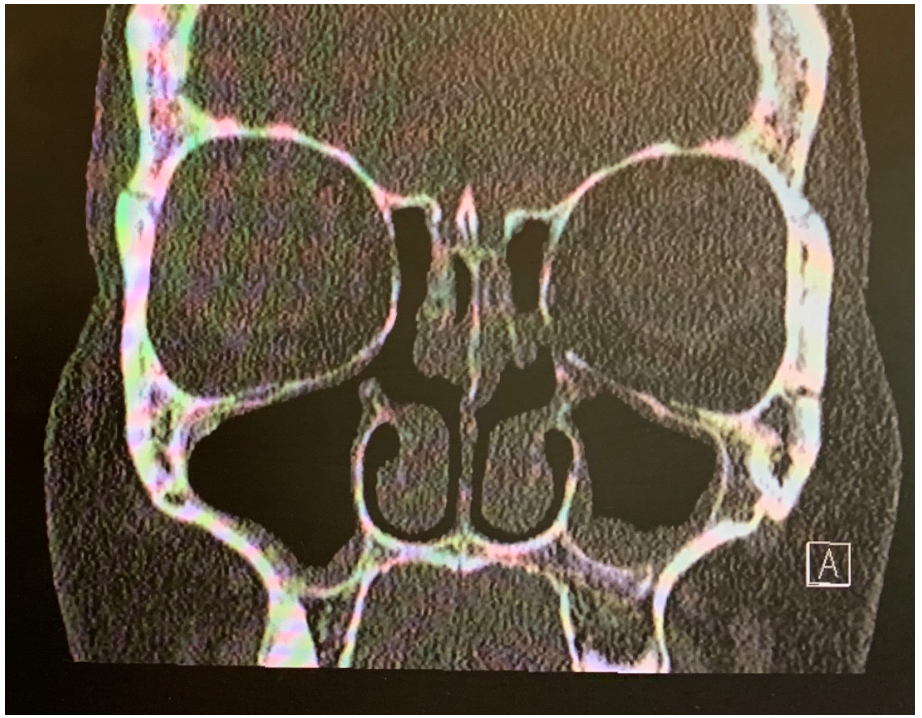


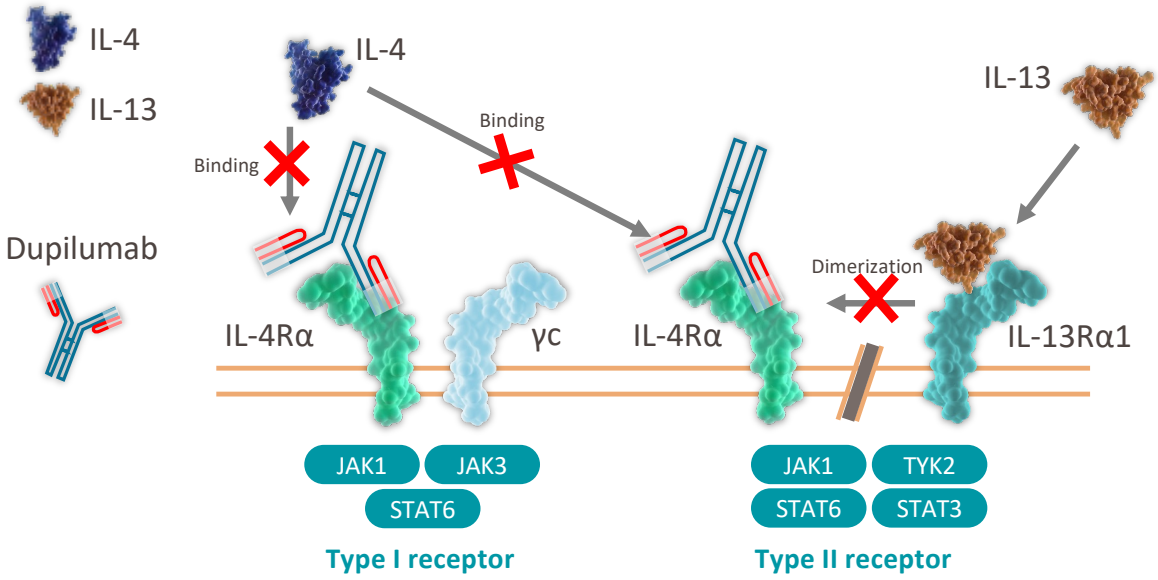
Credit: Martin Desrosiers MD, Montréal, QC, 2018

Dupilumab is a dual inhibitor of IL-4 and IL-13 signaling pathways[1,2]

1. IL-4 and IL-13 bind to receptors containing a shared subunit, IL-4Rα[1,2]

2. Dupilumab is a human monoclonal antibody that binds specifically to IL-4Rα, the shared receptor subunit for IL-4 and IL-13, thus inhibiting the dual signaling pathways of both IL-4 and IL-13[1,2]

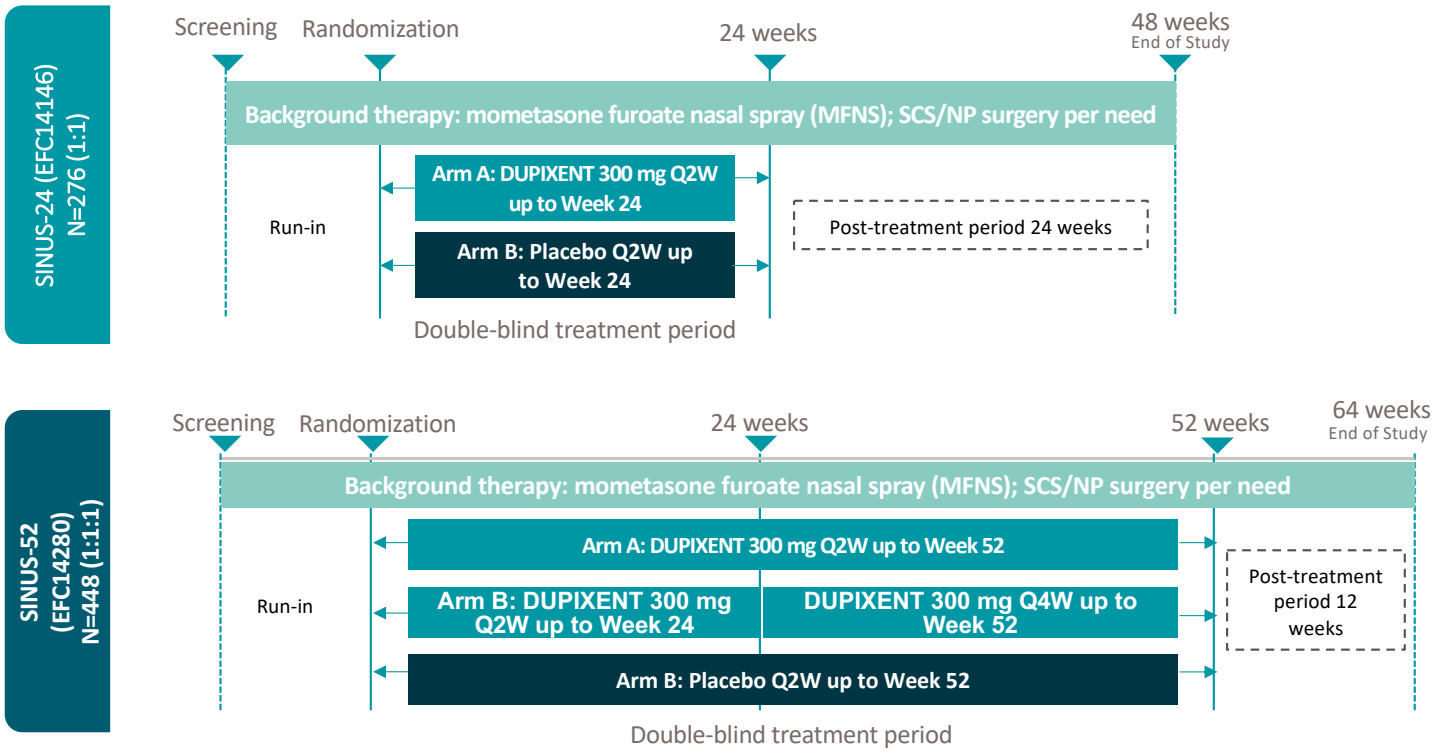
3. Dupilumab inhibits IL-4 signaling via the type I receptor and both IL-4 and IL-13 signaling through the type II receptor[1,2]



Expression of type 2 cytokines and chemokines and activation of additional inflammatory signaling pathways

1. Gandhi NA, et al. *Nat Rev Drug Discov.* 2016;15(1):35-50. 2. Le Floc'h A, et al. *Allergy*. 2020 May;75(5):1188-1204.

Phase III trials design in CRSwNP[1]

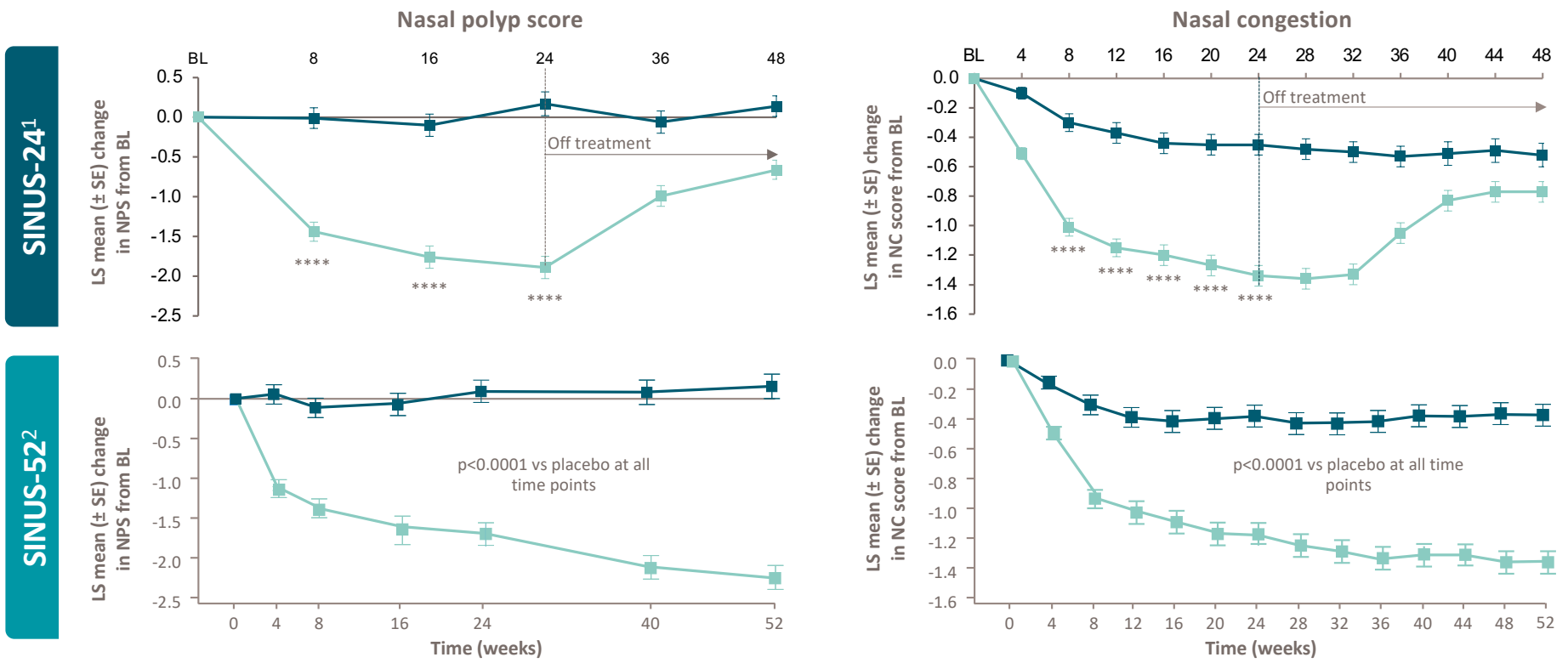


- **Primary endpoints**
  - NC at Week 24
  - NPS at Week 24
- **Selected key secondary endpoints**
  - LMK at Week 24
  - TSS at Week 24
  - UPSIT at Week 24
  - Loss of smell at Week 24
  - NPS at Week 52
  - NC at Week 52
  - SNOT-22 at Week 52
- **Pre-specified pooled analysis**
  - Proportion of patients requiring rescue with SCS or NP surgery
  - FEV1 at w24
- **Stratification factors**
  - Comorbid asthma (including NSAID-ERD)
  - Prior surgery
  - Country

*co-primary endpoint for Japan; **only available for SINUS-52

1. Bachert C, *Lancet* 2019; published online Sept 19. http://dx.doi.org/10.1016/S0140-6736(19)31881-1.

Dupilumab improved nasal polyp size and nasal congestion in patients with severe CRSwNP[1]



****p<0.0001

BL, baseline; CRSwNP, chronic rhinosinusitis with nasal polyps; LS, least squares; NC, nasal congestion; NPS, nasal polyp score; q2w, every 2 weeks; SE, standard error

1. Bachert C, *Lancet* 2019; published online Sept 19. http://dx.doi.org/10.1016/S0140-6736(19)31881-1.

EUFOREA position paper on biologics for treatment of CRS[1]

REVIEW

Allergy WILEY

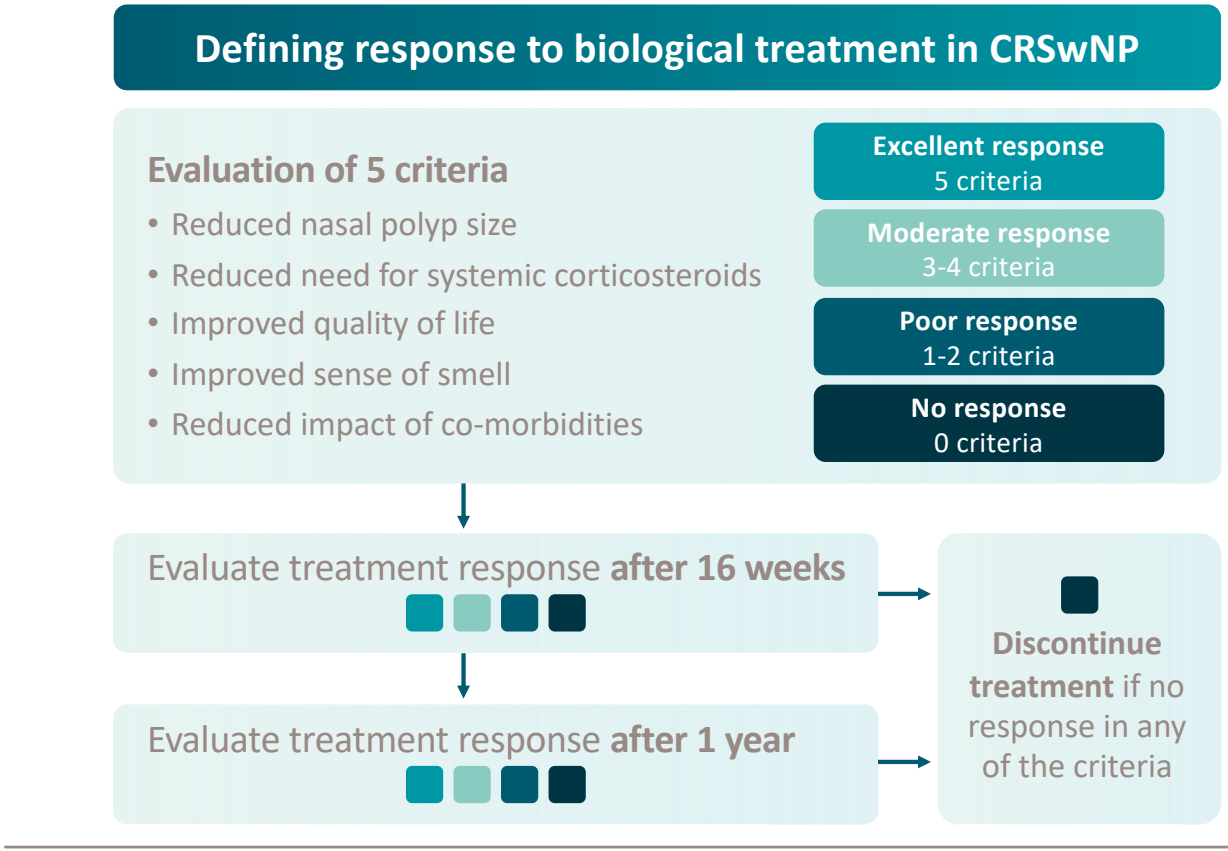
EUFOREA consensus on biologics for CRSwNP with or without asthma

Wytske J. Fokkens[1,2] | Valerie Lund[3] | Claus Bachert[2,4,5] | Joaquim Mullol[6] | Leif Bjermer[7] | Jean Bousquet[2,8] | Giorgio W. Canonica[9,10] | Lauren Deneyer[2] | Martin Desrosiers[11] | Zuzana Diamant[7,12,13] | Joseph Han[14] | Enrico Heffler[9,10] | Claire Hopkins[15] | Roger Jankowski[16] | Guy Joos[17] | Andrew Knill[18] | Jivianne Lee[19] | Stella E. Lee[20] | Gert Mariën[2] | Benoit Pugin[2,21] | Brent Senior[22] | Sven F. Seys[2,21] | Peter W. Hellings[1,2,21,23]

EUFOREA position paper on biologics for treatment of CRS[1]

1. Fokkens WJ, et al. *Allergy*. 2019 Dec;74(12):2312-2319.

Response criteria for biologicals in the treatment of CRS[1]



1. Fokkens WJ, et al. *Rhinology*. 2020 Suppl. 29: 1-464.

Positioning biologics: Who is the ideal patient?

- For the moment, suggested would be recurrent nasal polyposis despite surgery and therapy
  - Optimal medical treatment must remain within indications
- Demonstrated compliance with prior therapy
- Adequate surgery
- Trial period to assess effectiveness: Duration?
- What/when do we define failure and stop?
- Future: Biomarkers or optimal patient profiles