Acute and Chronic Rhinosinusitis: Current Trends in Diagnosis and Management

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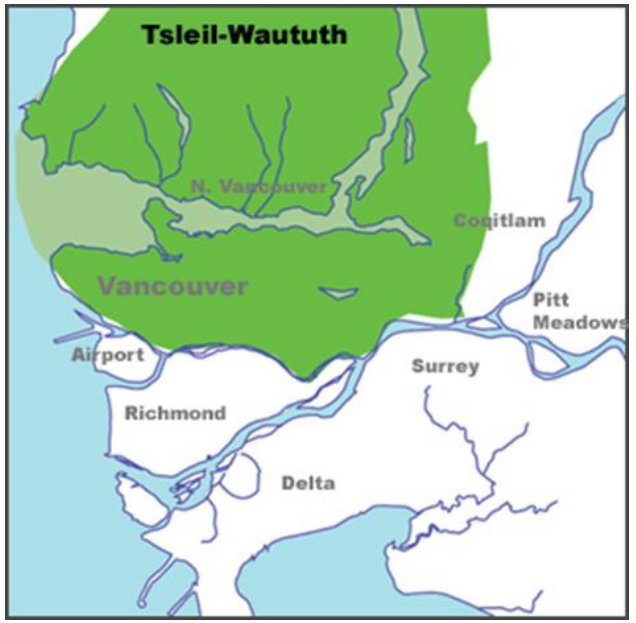
We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.



Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html

Consultant/Speaker:

Ondine Pharmaceuticals
Novartis Pharmaceuticals
SaNOtize Research and Development
CoMotion Inc
Astra Zeneca
GSK
Sanofi
iView Therapeutics

Rhinosinusitis
Economic Burden

- 2019: Overall expenditure attributable to sinusitis est. at $22 billion (U.S.)
- Prevalence of CRS: 12-14% (Asthma: 10%)
- An estimated 30 million cases dx annually in the US
- QOL:
  - worse than chronic heart failure and Parkinson's disease.
  - Poor mental health: Depression 77% higher
- *The total cost of diagnosing and treating sinusitis remains one of the most expensive chronic disorders experienced by the North American population and continues to increase yearly…*

Soler ZM, Wittenberg E, Schlosser RJ et al. Health state utility values in patients undergoing endoscopic sinus surgery. Laryngoscope 2011; 121: 2672-2678.

In the beginning…
it was a just a cold…

- **Sinus inflammation:**
  - often follows viral upper respiratory tract infections or allergic reactions:
    - *Congestion of sinus ostia (URTI, allergies) may predispose to ABRS*
  - occurs in 90% of individuals with the common cold
    - **Only 0.5% to 2% of these individuals will develop ABRS**
  - Colds that don't resolve over 7-10 days with worsening symptoms go on to become
    - ***Acute Bacterial Rhinosinusitis*** (ABRS).

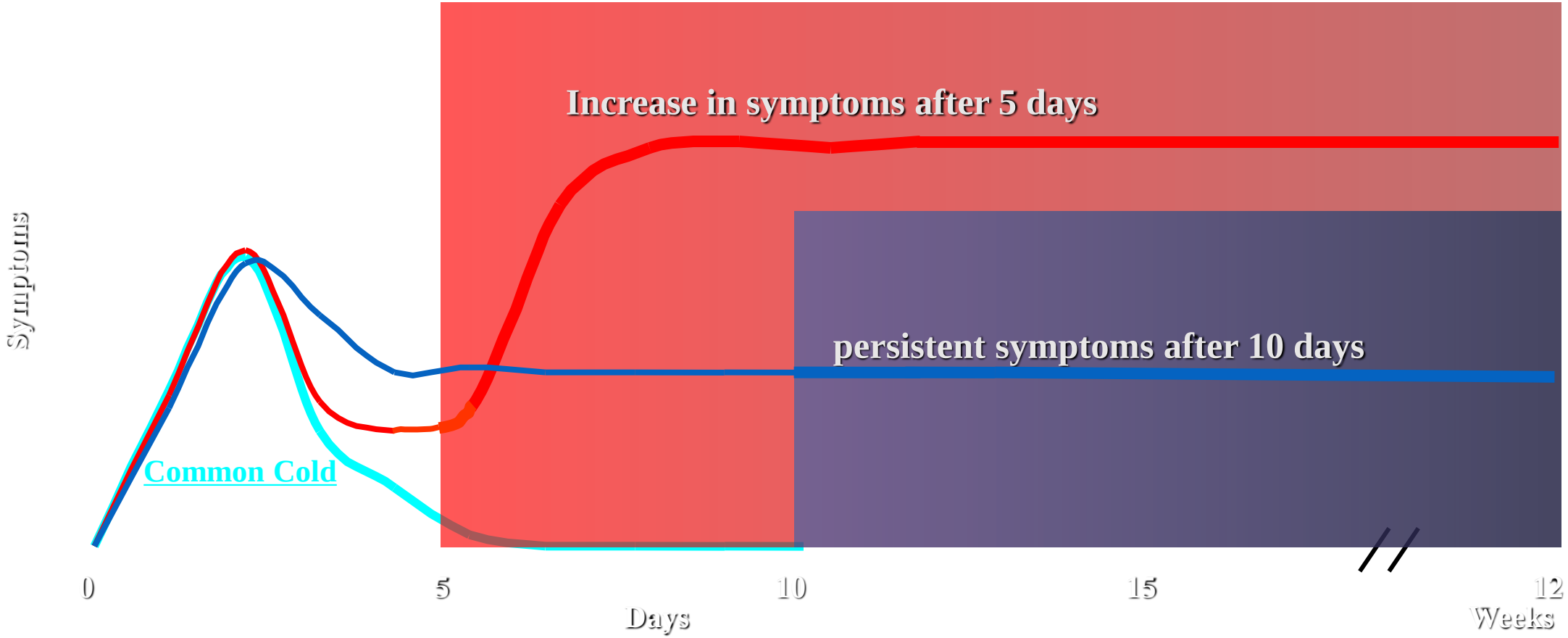
Definitions

- Acute RS: **> 7days and < 12 weeks.**
- Chronic RS: **> 12 weeks.**

- Recurrent Acute RS:
  - Four or more infections per year with complete resolution between infections
- Acute on Chronic RS

Acute rhinosinusitis: Definition

Increase in sy's after 5 days or persistent sy's after 10 days with less than 12 weeks duration



Adapted from Fokkens et al. EP3OS Guidelines. *Rhinol Suppl.* 2005;18:1.

Diagnosing ABRS

- Diagnosis based on clinical symptomatology
- Differential diagnosis:
  - Viral URTIs
  - Allergic rhinosinusitis

- Symptoms are non-specific & similar to viral URTIs and Allergic Rhinitis:

Symptoms ABRS

Symptoms of ABRS

Major	Minor
Facial pain/pressure/fullness	Headache
Nasal obstruction	Halitosis
Nasal purulence/discolored postnasal discharge	Fatigue
Hyposmia/anosmia	Dental pain
	Cough
	Ear pain/pressure

ABRS Diagnosis

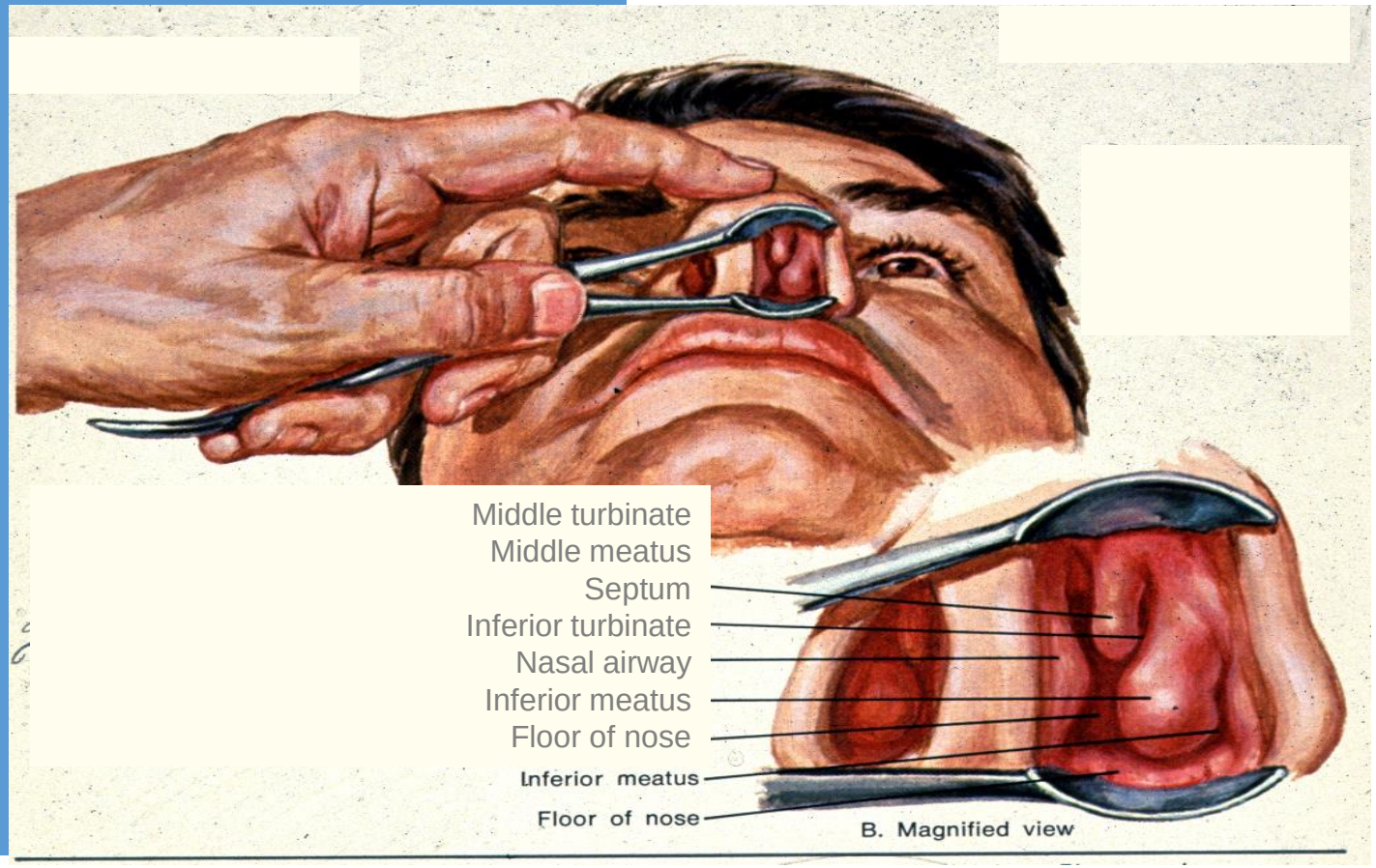
ABRS Diagnosis Requires the Presence of at Least 2 Major Symptoms*

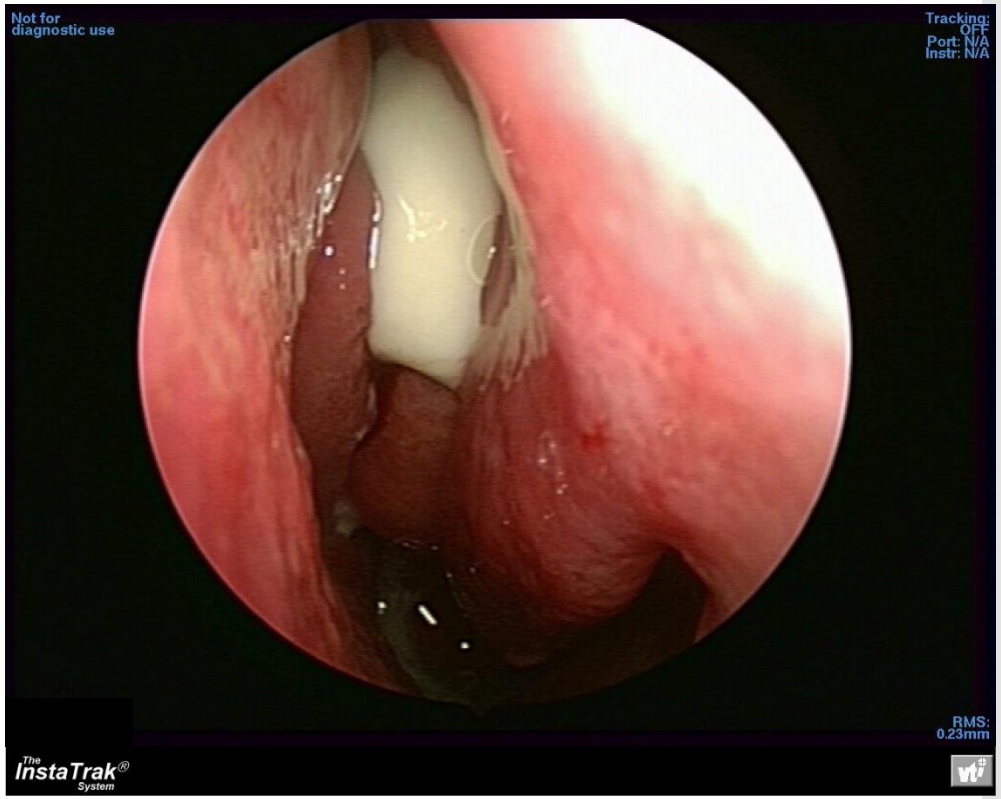
	Major Symptom
P	Facial **P**ain/pressure/fullness
O	Nasal **O**bstruction
D	Nasal purulence/discolored postnasal **D**ischarge
S	Hyposmia/anosmia (**S**mell)

PODS

*At least 1 symptom must be nasal obstruction or nasal purulence/discolored postnasal discharge. Thus, a diagnosis requires at least 2 PODS, one of which must be O or D.

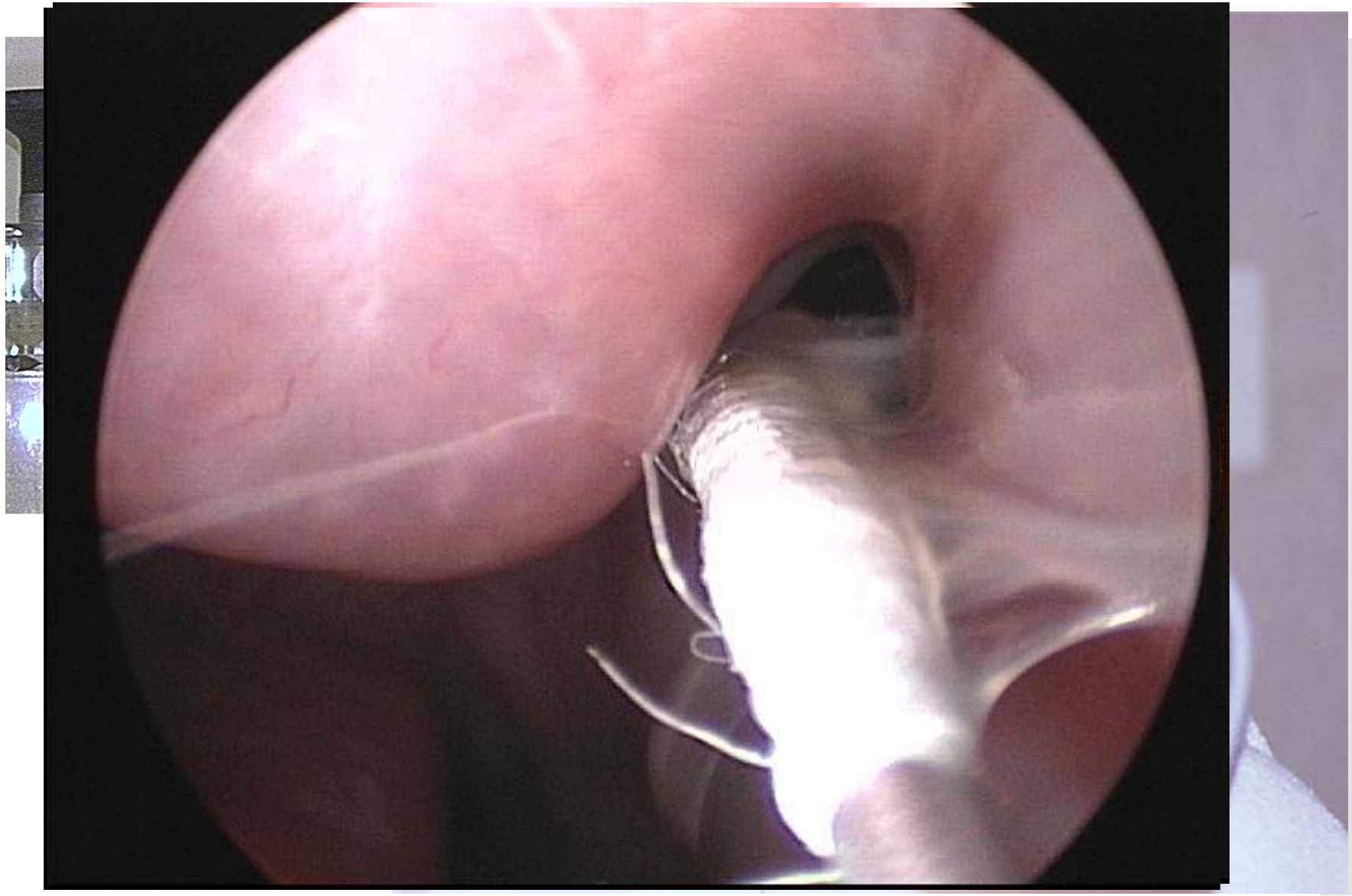
Examination:





- Adequate ability to use a nasal speculum and headlight.
- Recognizing the anatomy

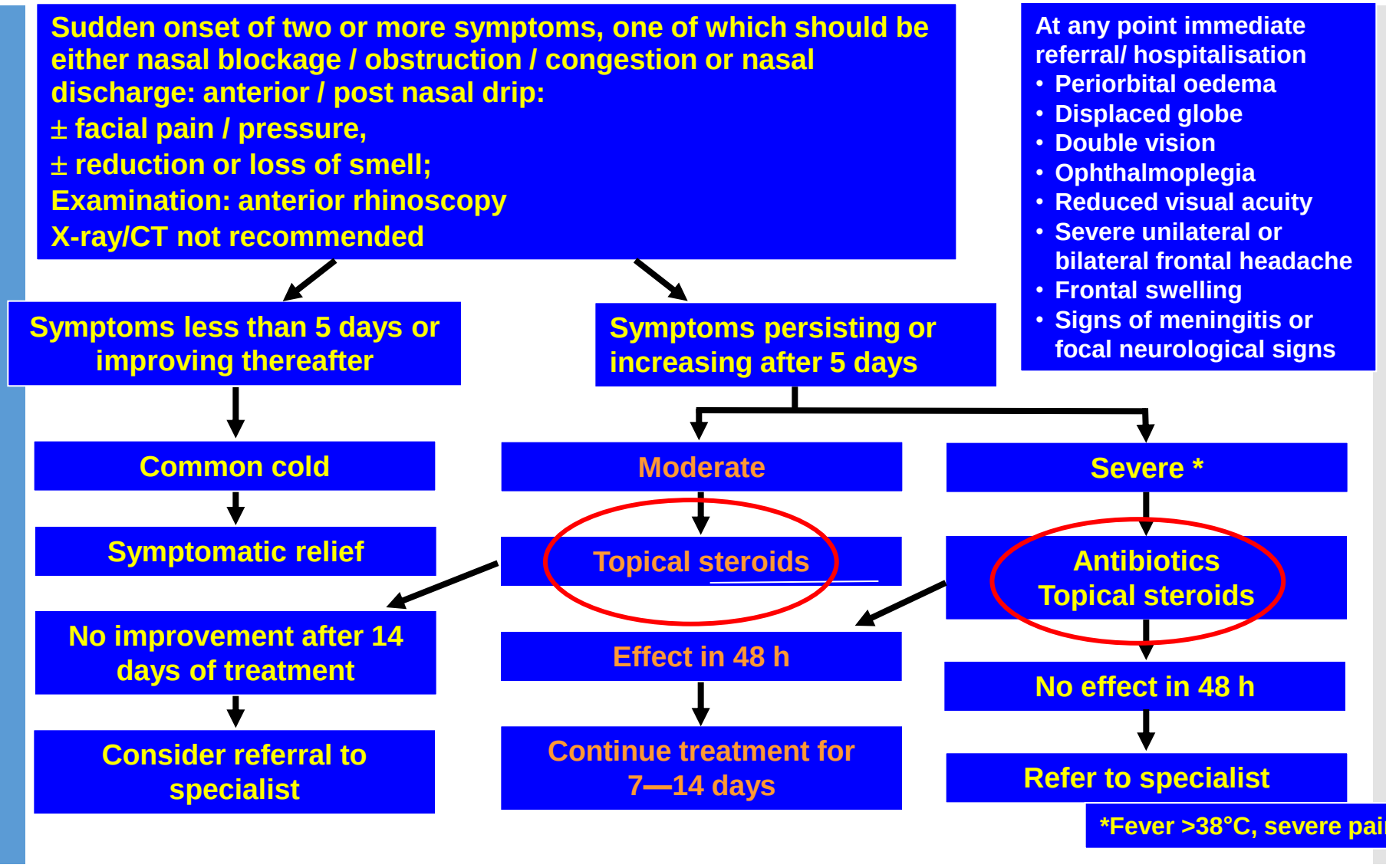
Rhinologist Examination



Imaging in A&CRS

- Sinus XR: NEVER
- Sinus CT:
  - Modality of Choice
  - NOT for ABRS
  - For failed medical therapy/CRS/Surgical Planning
- MRI:
  - Not indicated
  - Tumor excision planning (intracranial/orbital)

Management Scheme: ABRS

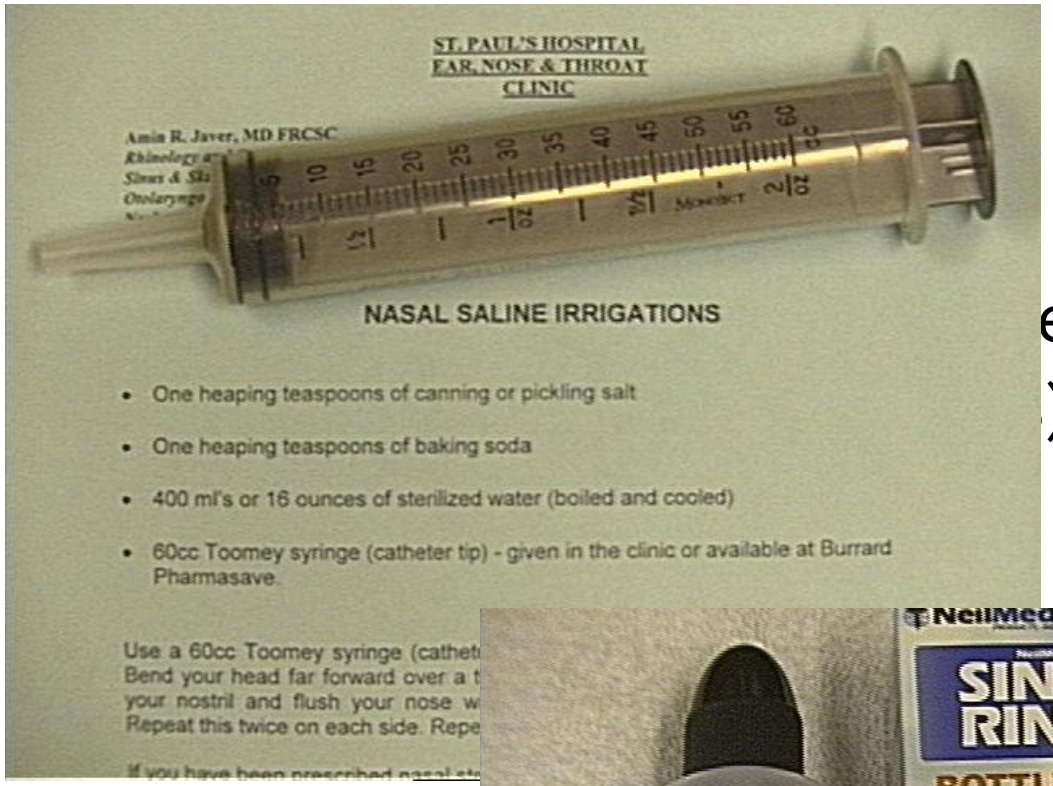


Urgent Referral

- Complications of ABRS can elicit a Medical Emergency:
  - Systemic Toxicity
  - Altered mental status
  - Severe Headache
  - Swelling of Orbit or change in Visual Acuity

- **Orbital Cellulitis:**
  - Most common complication of ABRS

Non-Medical Management



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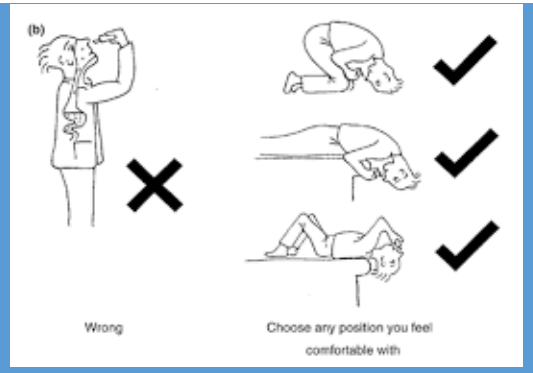
etc.)



Medical Management

- **Topical nasal steroids (eg Mometasone):**
  - Reduces inflammation in OMC
  - Indicated as first line for mild/moderate uncomplicated ABRS
- **Antibiotics:**
  - Little evidence that they help significantly for ABRS.
  - 1st line: Amoxicillin (TMP/SMX or macrolide)
    - When QOL/productivity ⬇
    - When severe sinusitis or comorbidities
    - **Not for mild/mod ABRS**

Other Adjunctive Therapies

- Oral/Topical Decongestants:
  - For symptomatic relief only.
  - No longer than 72h (potential for rebound)
- Antihistamines:
  - No benefit in ABRS (only for allergic rhinitis)
- Mucolytics:
  - Guafenesine/N-AC
    - Some benefit in one study.
- Complementary/Alternative Medicine:
  - Vitamin C/Zinc lozenges: mixed results
  - Echinacea: some positive effects.
  - Sinfrontal: PRCT showed benefit.
  - Colloidal Silver

Diagnosis of CRSwNP Requires a Multidisciplinary Approach and Should Combine Assessment of Presenting Symptoms and Objective Measures

Symptoms[1,2]

Inflammation of the nose and paranasal sinuses characterized by ≥2 symptoms for ≥12 weeks:

- Nasal blockage/obstruction/congestion
- Anterior/posterior nasal discharge/drip
- Facial pain/pressure
- Reduction/loss of smell

+

Objective measures[1,2]

Any of the following:

Endoscopic signs

- Nasal polyps
- Mucopurulent discharge
- Edema/mucosal obstruction

CT signs

- Mucosal changes

Nasal polyps

Mucosal thickening

Diagnosis of CRSwNP should be based on symptoms and objective evidence of disease as symptoms are non-specific and can overlap with other upper respiratory diseases[3]

CT, computed tomography

1. Fokkens WJ, et al. *Rhinology*. 2012;50(Suppl. 23):1–298;
2. Orlandi RR, et al. *Int Forum Allergy Rhinol*. 2016;6(Suppl.1):S22–S209;
3. Hoffmans R, et al. *BMC Fam Pract*. 2015;16:120

Chronic Rhinosinusitis

- Diagnosis = Presence of symptoms + objective finding (endoscopy or CT)
- Symptoms:
  - Lesser intensity than ABRS
  - Duration exceeds 12 weeks
  - PND, dull headaches, fatigue, cough, adult onset asthma
  - "The cold that never went away"
- Asthma co-occurs in 40-70% of CRS patients (united airway theory)

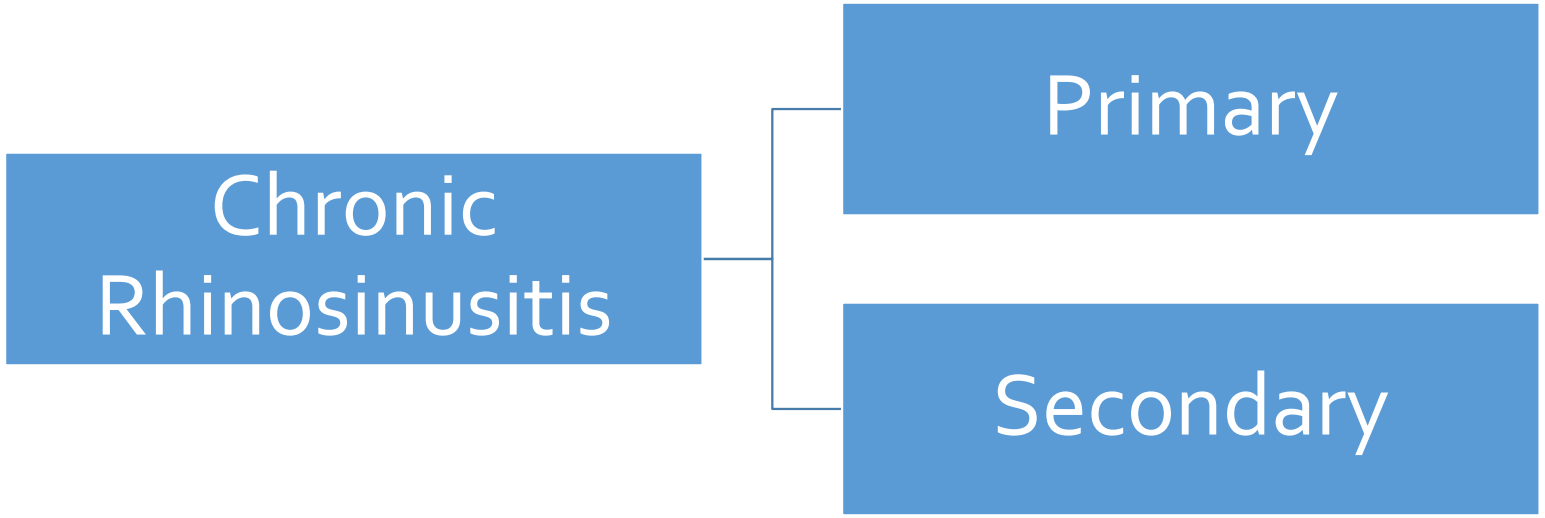
CRS

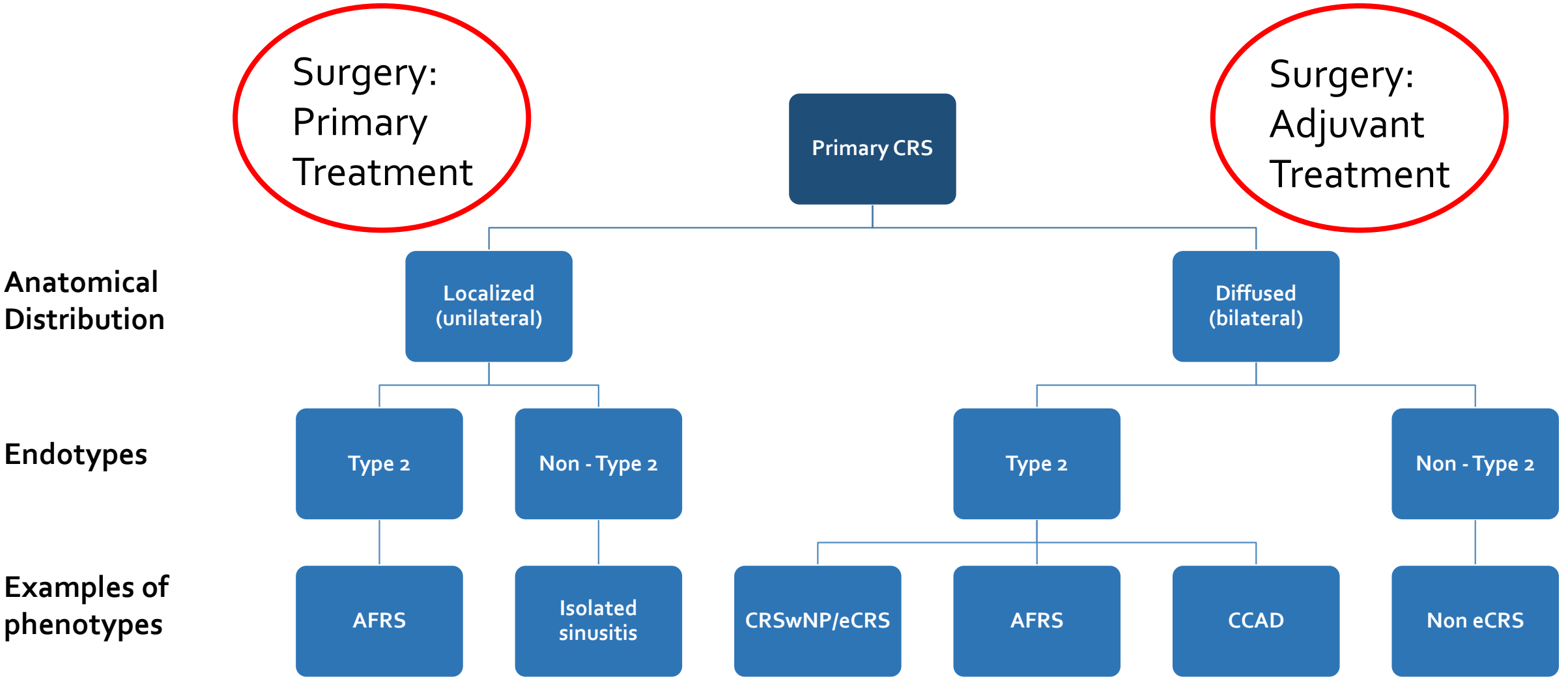
- A **syndrome** rather than a disease.
- An **umbrella** term for several inflammatory disease states of the sinonasal cavities.
- Characterized by:
  - tissue remodeling and mucosal inflammation
  - **Multiple inflammatory pathways that interact dynamically leading to *variable patterns of tissue inflammation***.
- Only 'roughly' correlates to clinical phenotype

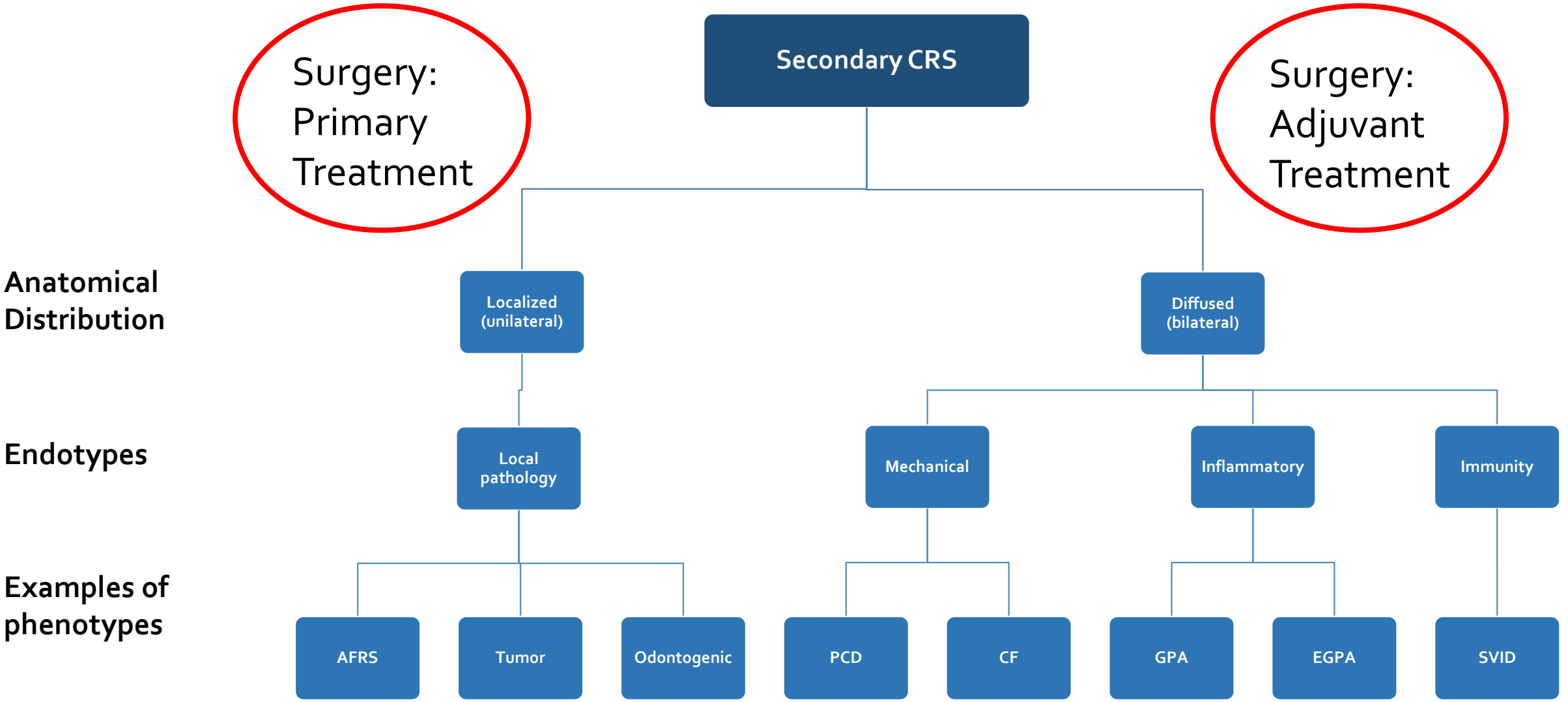
CRS: a little history…

- **Initially:** 2 major phenotypes (reflected at molecular level):
  - **CRSwNP (Th2/Eos) and**
  - **CRSsNP (Th1 cells)**
- Simple differentiation into TH1 and TH2 did **NOT** encompass molecular diversity in CRS.
- **Now: T2 vs Non-T2 Inflammation**
- **New classification system…**

*A **New*** CRS Classification EPOS 2020




Surgery: Primary Treatment
Surgery: Adjuvant Treatment
Primary CRS
Anatomical Distribution
Localized (unilateral)
Diffused (bilateral)
Endotypes
Type 2
Non - Type 2
Type 2
Non - Type 2
Examples of phenotypes
AFRS
Isolated sinusitis
CRSwNP/eCRS
AFRS
CCAD
Non eCRS


Surgery: Primary Treatment
Secondary CRS
Surgery: Adjuvant Treatment
Anatomical Distribution
Endotypes
Examples of phenotypes
Localized (unilateral)
Diffused (bilateral)
Local pathology
Mechanical
Inflammatory
Immunity
AFRS
Tumor
Odontogenic
PCD
CF
GPA
EGPA
SVID

CRS Diagnosis

CRS Diagnosis Requires the Presence of at Least 2 Major Symptoms*

	Major Symptom
C	Facial **C**ongestion/fullness
P	Facial **P**ain/pressure/fullness
O	Nasal **O**bstruction/blockage
D	Purulent anterior/posterior nasal **D**rainage (discharge may be nonpurulent, nondiscolored)
S	Hyposmia/anosmia (**S**mell) [9,21,136].

CPODS

*A diagnosis requires at least 2 CPODS, present for 8 to 12 weeks, plus evidence of inflammation of the paranasal sinusus or nasal mucosa.

CRS is diagnosed on clinical grounds but must be confirmed with at least 1 objective finding on endoscopy or CT scan.

CRS Management

- Adequate Medical Management:
  1. **Antibiotics:**
     - 8-12 weeks of low dose long term macrolides
     - 250mg po bid X 8-12 weeks (no cardiac issues)
  2. **Short course of Oral Corticosteroids:**
     - Prednisone 30mg po qam X 1 week, 20mg X1wk, 10mg po X 1 week.
  3. **Topical Nasal Steroids:**
     - Pulmicort in saline rinse
       - Add 1mg (2ml nebules) in 240ml saline and rinse daily
- Success rate of medical management ⬇

CRS Management

- Most CRS patients respond to medical management
  - Nasal corticosteroids
  - Nasal irrigations
- Surgical (ESS) management:
  - Only for those who fail medical management.
  - Most respond favorably to ESS
  - ***17% failure rate that need revision surgery.***

Surgical Success

- Surgical success rates have improved drastically with improvements in:
  1. Understanding of anatomy, physiology and
  2. Advances in technology: Image Guided FESS, Instrumentation, Camera's, Scopes, etc
  3. Improvement in postoperative care.
  4. *Development of centres dedicated to the treatment of sinus disease (SPSC).*

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Success in FESS?

- **FESS strongly Associated with improvement in:**
  1. CRS symptoms
  2. QoL
  3. Sleep
  4. Cognitive Dysfunction
  5. *…and more*

But in 5-10%…

Recalcitrant CRS

- Patients with chronic rhinosinusitis (CRS) that fail maximal medical and surgical therapy are categorized as **recalcitrant (rCRS)**
- **Several factors can lead to rCRS**
  - Type 2 inflammation
  - Biofilms and dysbiosis

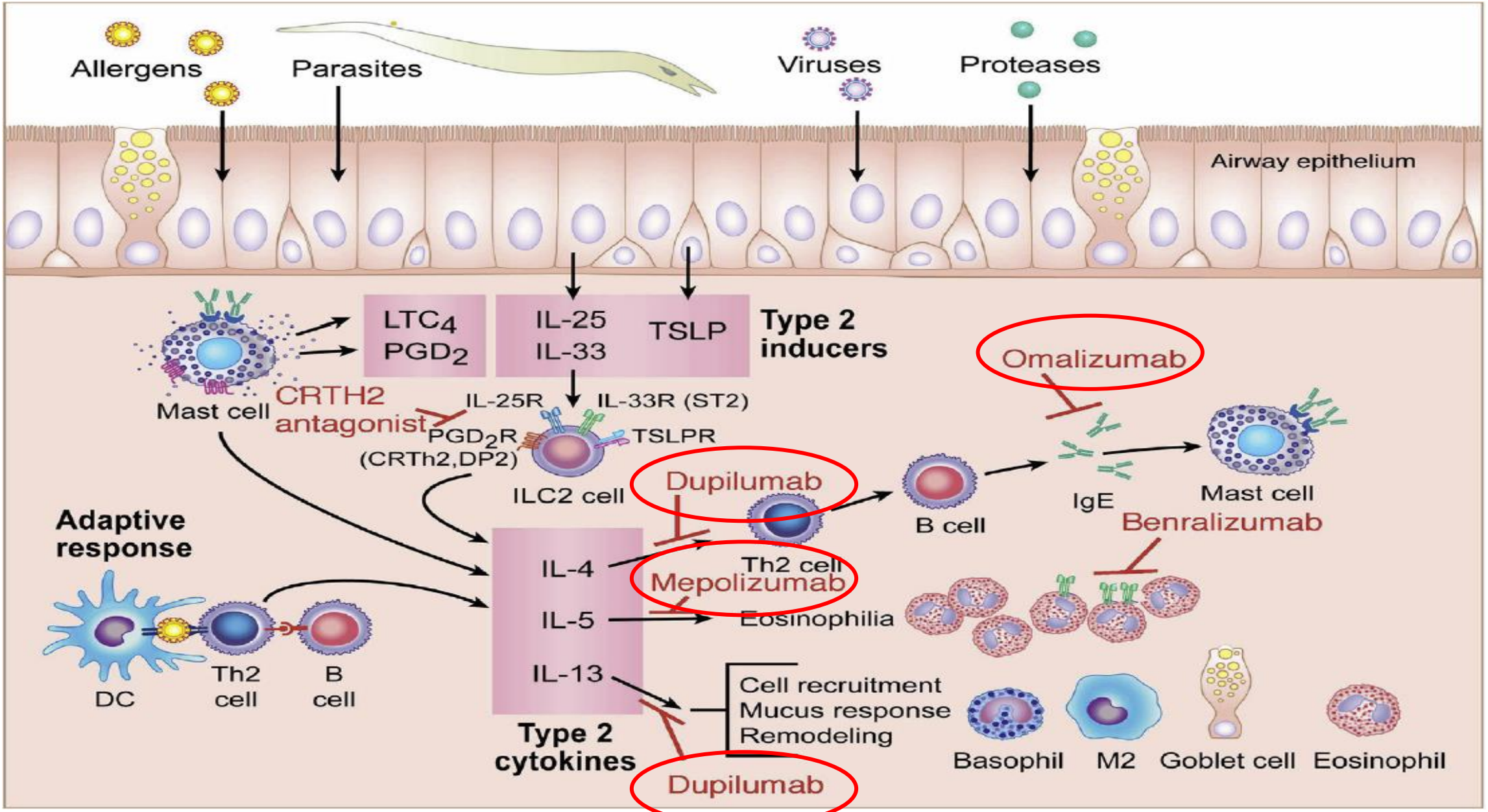
≠

Systemic and antibiotics, antiseptic rinses (e.g., betadine), and/or advanced aeration surgery

Current Treatment Strategies

- ***What is the latest in management for these patients?***

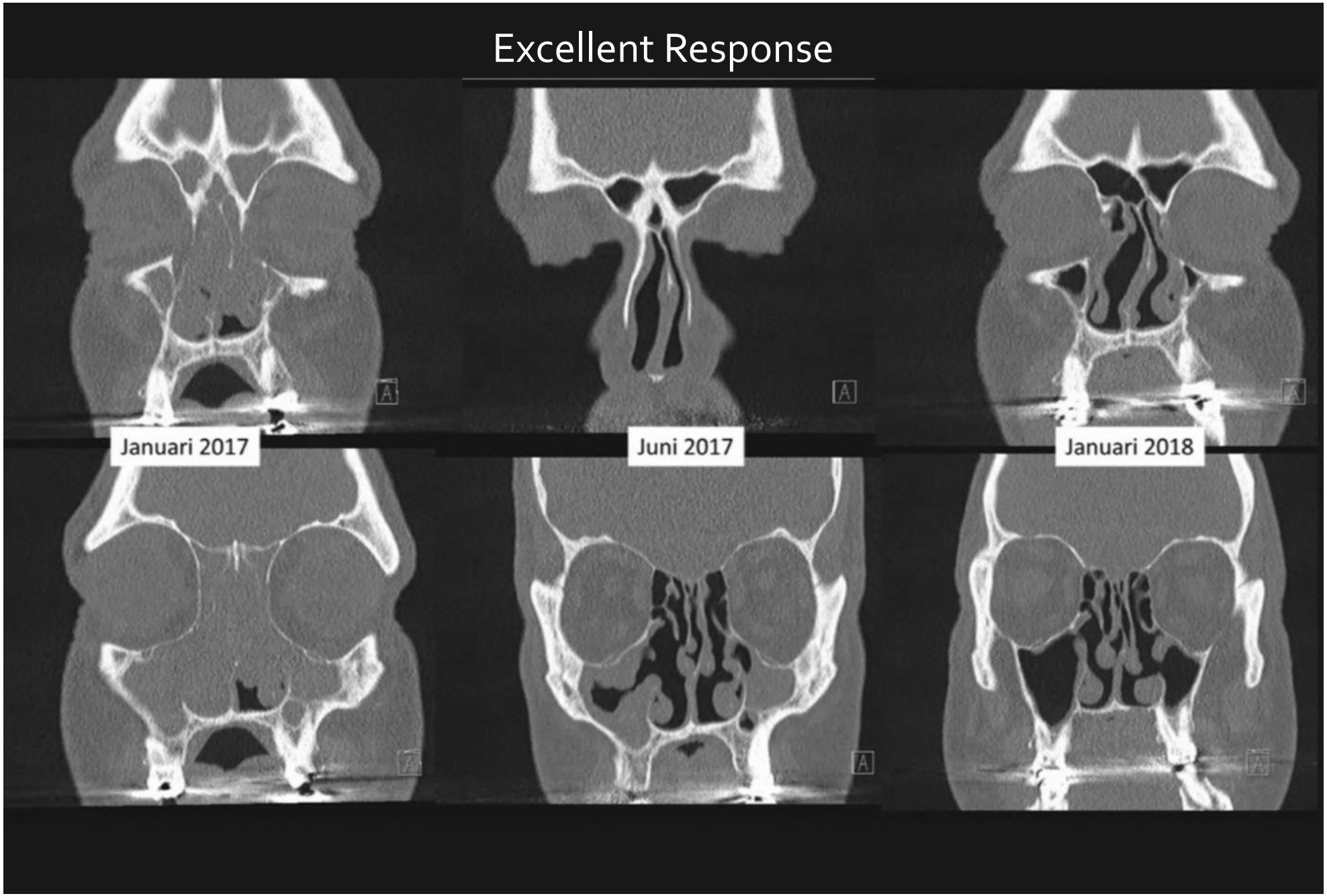
Monoclonal ab's targeting type 2 inflammatory processes in CRSwNP patients.



Adapted from Hulse et al.95(p341) Illustration courtesy of Dr Robert Schleimer.

	Dupilumab	Omalizumab	Mepolizumab	Benralizumab
Pharmacology	Fully human monoclonal antieIL-4 receptor alpha subunit antibody	Recombinant humanized monoclonal anti-IgE antibody	Recombinant humanized monoclonal antieIL-5 antibody	Recombinant humanized monoclonal antieIL-5 receptor alpha subunit antibody
Indications	Moderate to severe asthma with eosinophilic phenotype or with oral corticosteroide dependent asthma, atopic dermatitis, **CRSwNP** **Approved in N. America August 2020**	Moderate to severe asthma with positive allergy testing, chronic urticaria	Severe asthma with eosinophilic phenotyAdapted from Hulse et al.95(p341) Illustration courtesy of Dr Robert Schleimer. pe, eosinophilic granulomatosis with polyangiitis	Severe asthma with eosinophilic phenotype
Clinical trials to date	Phase 2 and 2 phase 3 trials SINUS-24 and SINUS-52 observed reduced NP size, improved symptoms including nasal congestion, smell, and SNOT-22	2 RCTs observed decreased polyp size, improved symptoms in those with comorbid asthma.90,91 Phase 3 trials POLYP1 and POLYP2 observed reduced NP size, improved symptoms including nasal congestion, smell, and SNOT-22	2 RCTs observed decreased polyp size, improved smell and SNOT-22, and reduced need for surgery. Phase 3 studies ongoing	Phase 3 studies pending

Excellent Response



Nucala helps prevent repeat nasal polyps surgery[1,2]

In patients with refractory-to-treatment nasal polyps (study population, n=407):

57% reduction in need for surgery vs. placebo[1*]

Secondary endpoint: time to nasal polyps surgery; results at Week 52, HR: 0.43, 95% CI: 0.25, 0.76; p=0.0032. Nucala: n=18/206; placebo: n=46/201.[1]

In patients with refractory-to-treatment nasal polyps with ≥300 eosinophils/µL (n=278):

69% reduction in need for surgery vs. placebo[2†]

Post hoc analysis: results at Week 52: HR: 0.31, CI: 0.15, 0.64. Nucala: n=10/139 vs. placebo: n=35/139.[2]

[*]SYNAPSE is a 52-week, randomised, double-blind, parallel group Phase III study assessing the clinical efficacy and safety of Nucala 100mg SC as an add-on to maintenance treatment in adults with severe bilateral nasal polyps, compared to placebo. Need for surgery based on time to nasal polyps surgery. Need for surgery based on time to nasal polyps surgery. Secondary endpoint: time to first nasal polyps surgery within the study. At Week 52, 18/206 (9%) participants treated with Nucala had had surgery vs. 46/201 (23%) with placebo. For the purpose of this study, nasal polyps surgery was defined as any procedure involving instruments resulting in incision and removal of tissue or dilation of the air passages in the nasal cavity.[1]
[†]Post hoc subgroup analysis in participants with ≥300 cells/µL. At Week 52, 10/139 (7%) participants treated with Nucala had had surgery vs. 35/139 (25%) with placebo.[2]
CI, confidence interval; HR, hazard ratio; VAS, visual analogue scale.
References: 1. Han JK *et al. Lancet Respir Med.* 2021; published online April 16. 2. Bachert C *et al*. ACAAI 2020. Poster no. P503.

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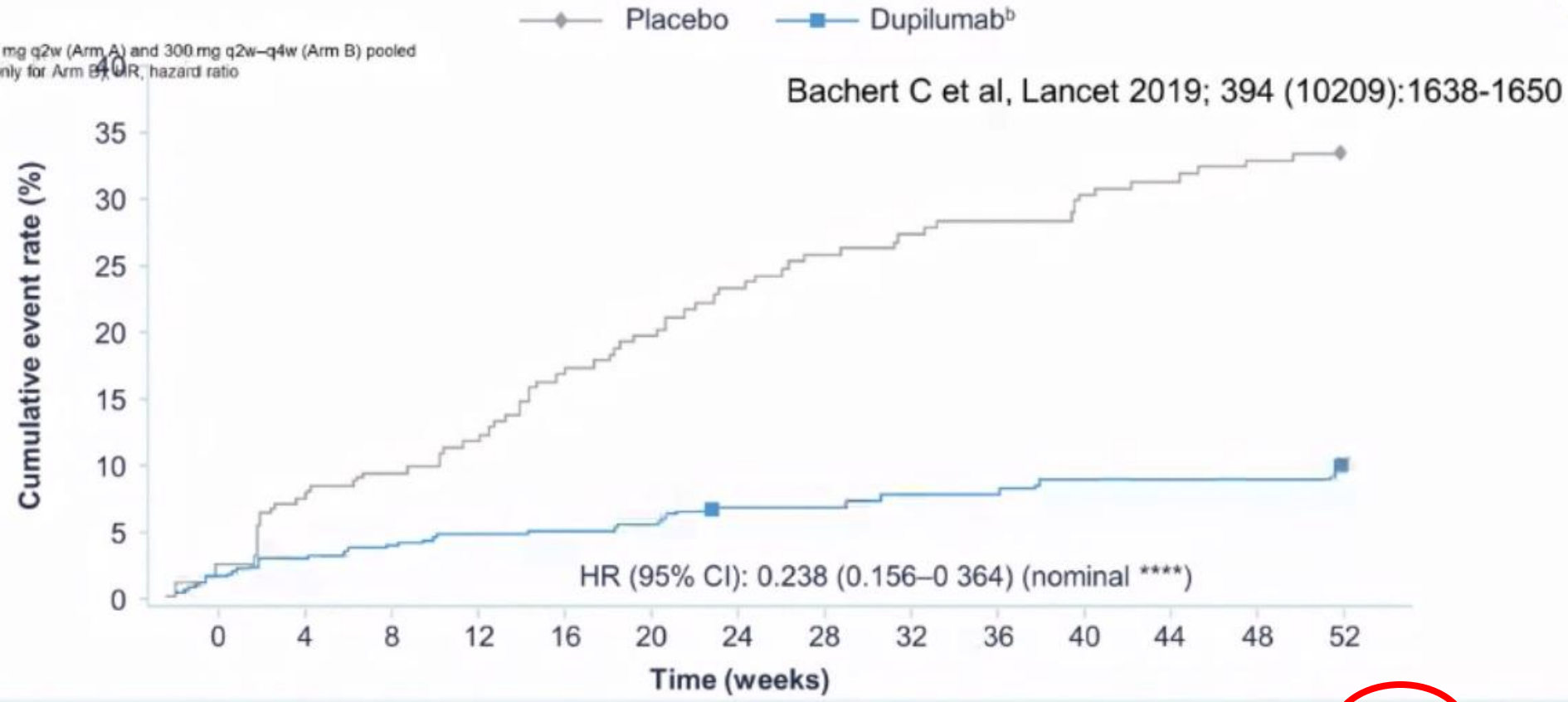
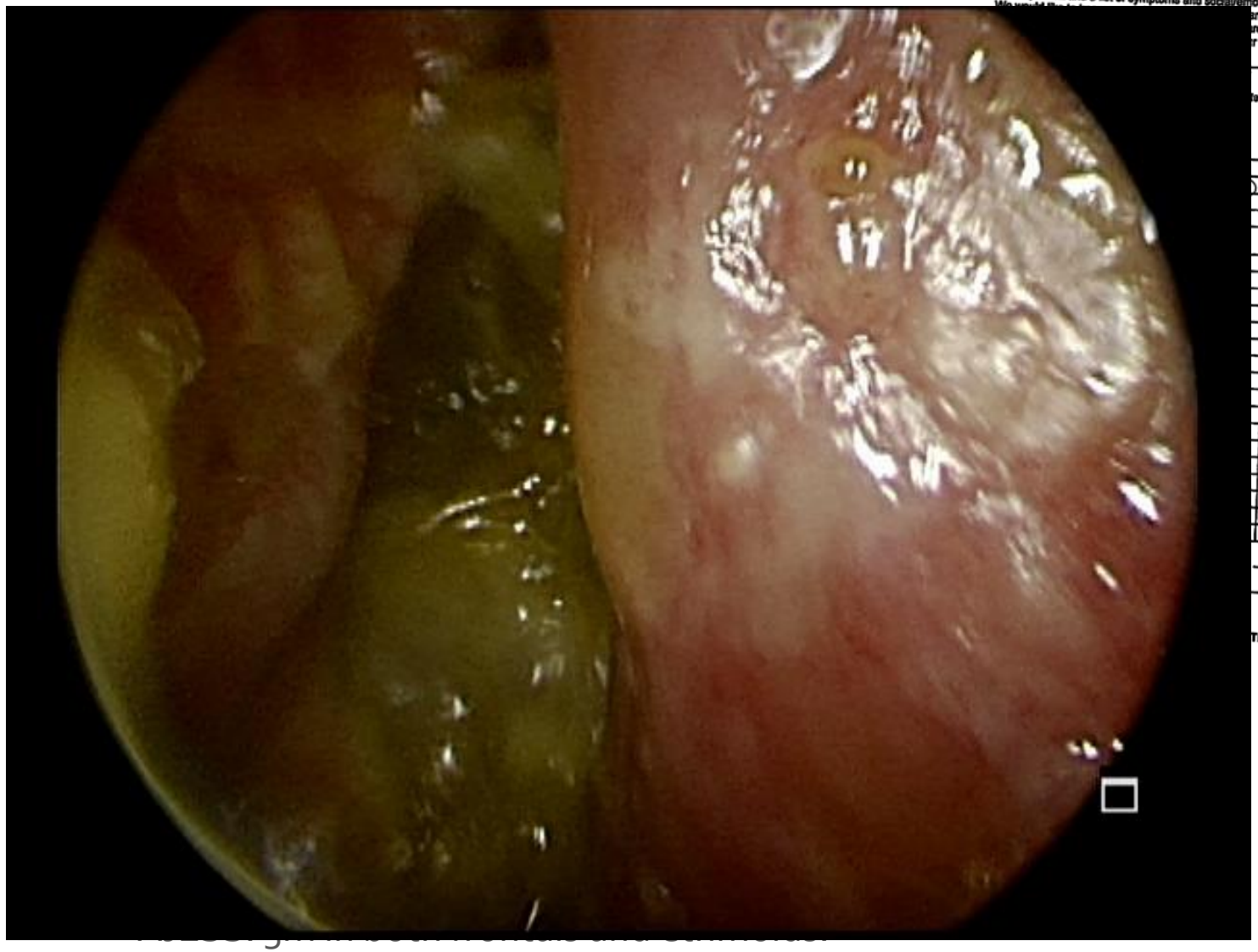
Dupilumab SC: Time to First SCS Use and/or NP Surgery Over 52 Week Treatment Period (Phase 3 SINUS-52)

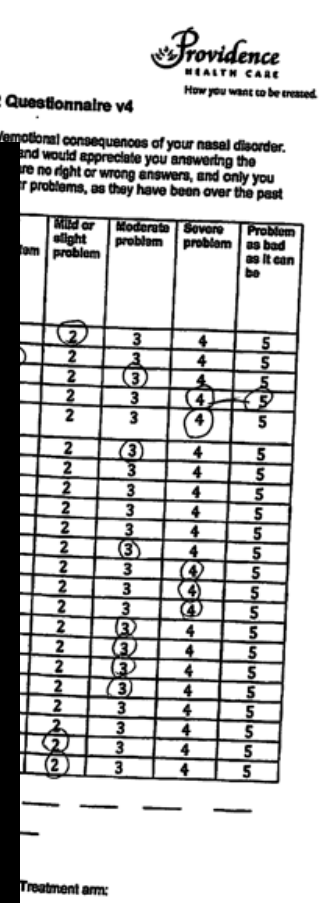
****p<0.0001
[b]Dupilumab 300 mg q2w (Arm A) and 300 mg q2w–q4w (Arm B) pooled (first 24 weeks only for Arm B); HR, hazard ratio



Dupilumab 300 mg q2w vs placebo reduced the proportion of patients requiring SCS by 74.6%, and the proportion requiring nasal polyp surgery by 89.4%

Case:
Mr. GT
54 yo M





Sino-Nasal Outcome Test-22 Questionnaire v4

Providence HEALTH CARE

How you want to be treated.

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. ...and would appreciate you answering the ...re no right or wrong answers, and only you ...r problems, as they have been over the past

	Mild or slight problem	Moderate problem	Severe problem	Problem as bad as it can be
	(2)	3	4	5
	2	(3)	4	5
	2	(3)	4	5
	2	3	(4)	5
	2	3	(4)	5
	2	(3)	4	5
	2	3	4	5
	2	3	4	5
	2	3	4	5
	2	3	4	5
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	2	(3)	4	5
	2	3	4	5
	(2)	3	4	5
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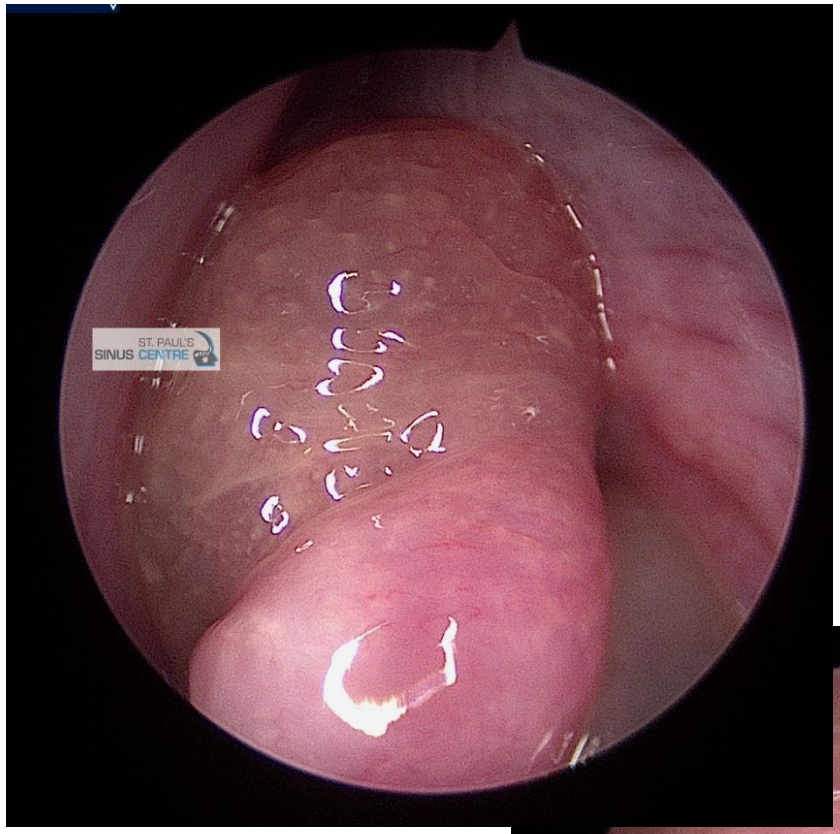
	(2)	3	4	5

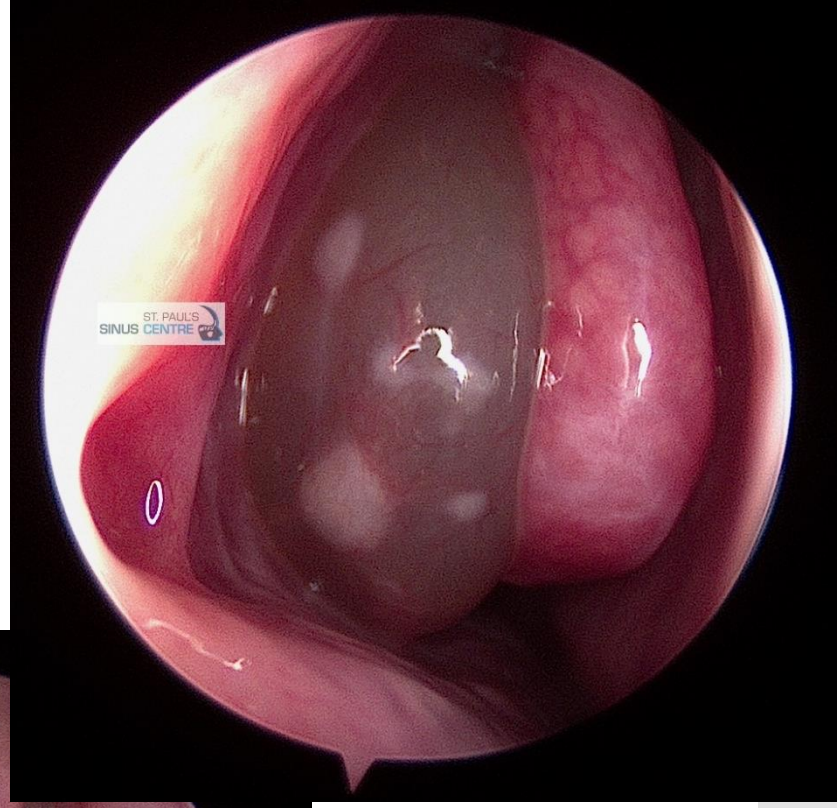
Treatment arm:

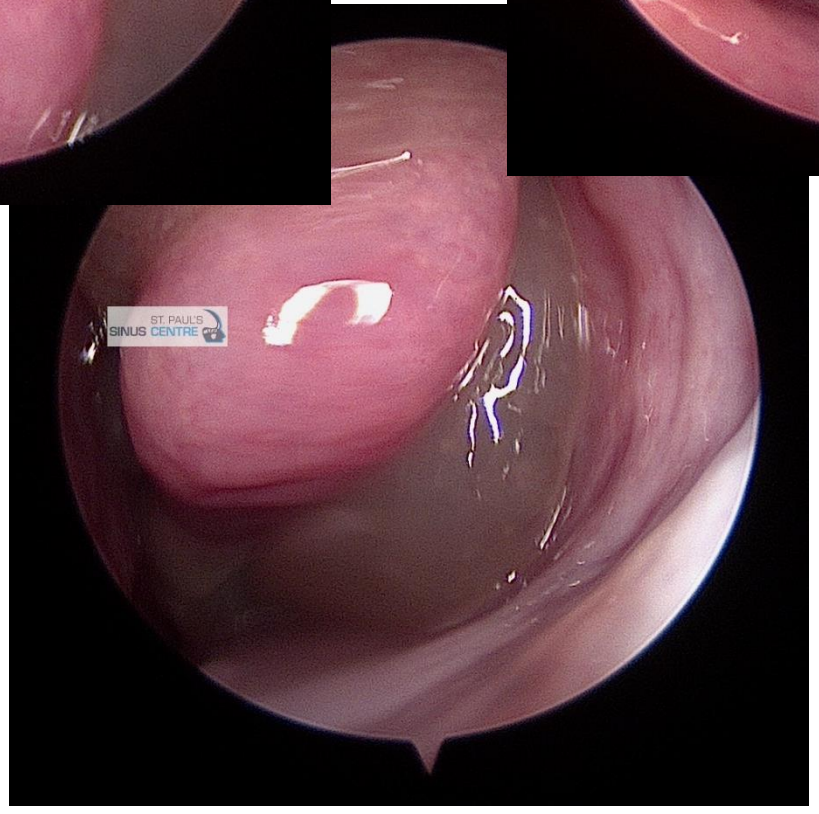
53/110

Case:
Mr. GT
54 yo M

Pre-Mepolizumab







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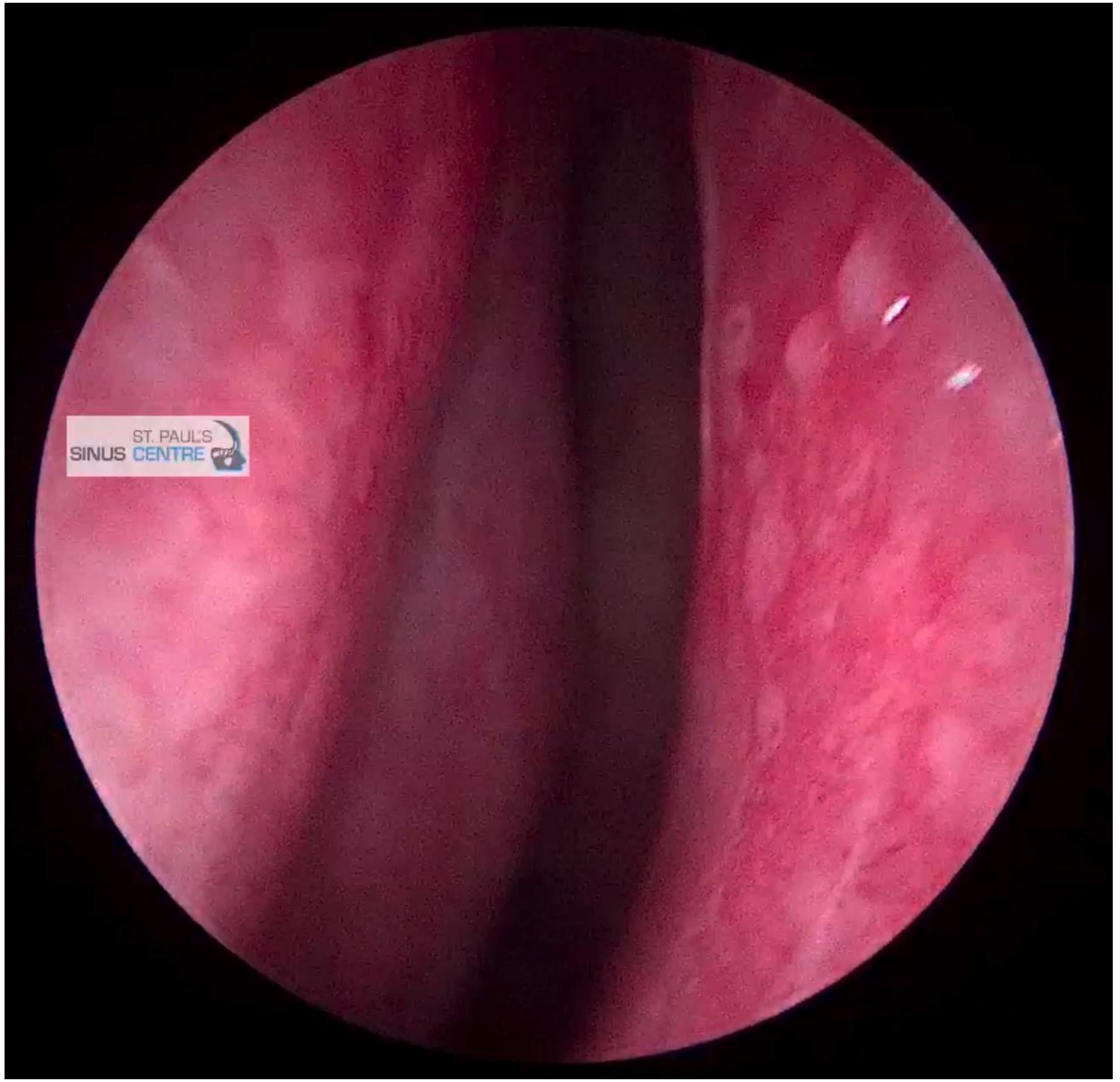
Post-Mepolizumab



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Thamboo *et al. Journal of Otolaryngology - Head and Neck Surgery* (2021) 50:15
https://doi.org/10.1186/s40463-021-00493-2

Journal of Otolaryngology - Head & Neck Surgery

ORIGINAL RESEARCH ARTICLE Open Access

Canadian Rhinology Working Group consensus statement: biologic therapies for chronic rhinosinusitis

Andrew Thamboo[1*], S. Kilty[2], I. Witterick[3], Y. Chan[3], C. J. Chin[4], A. Janjua[1], A. Javer[1], J. Lee[3], E. Monterio[3], B. Rotenberg[5], J. Scott[4], K. Smith[6], D. D. Sommer[7], L. Sowerby[5], M. Tewfik[8], E. Wright[9] and M. Desrosiers[10]

11 consensus statements

1. Patients must have both subjective and objective findings consistent with the diagnosis of CRSwNP to qualify for biologic therapy. All endotypes of CRSwNP are considered eligible except for primary ciliary dyskinesia and cystic fibrosis

*2. Patients with CRSwNP do **not** need another Type 2 inflammatory condition such as asthma to be considered for biologic therapy*

3. There is insufficient evidence to make a recommendation for providing biologics to patients with CRSsNP.

4. Biologics should not be provided to those suffering with recurrent acute bacterial sinusitis.

*5.The severity of subjective CRS symptoms needs to be **moderate to severe** based on the clinicians choosing of a validated patient reported outcome measure for chronic sinus disease.*

6. Biologics should only be considered for those who have undergone adequate sinus surgery and failed appropriate medical therapy (AMT) following surgery. Patients unfit for surgery who have failed AMT may also be considered candidates for biologic therapy.

7. Option: A CT sinus scan performed prior to administration of biologics may determine if adequate sinus surgery was performed and to objectively confirm global mucosal inflammation.

*8. Response to biologics is based on subjective and objective improvement; sense of smell, nasal obstruction, nasal discharge and facial pain. Objective improvement: on endoscopy or CT scan by **16 weeks and reevaluated at 1 year.***

*9-Providers have the option of providing another biologic therapy(**switching)***

10-Cost of biologics matters in the decision making of the use of biologics for CRS patients ($600 to $4000 per vial)

11- The short-term use of biologics (12 months) in CRSwNP is considered safe (up to 52 weeks)

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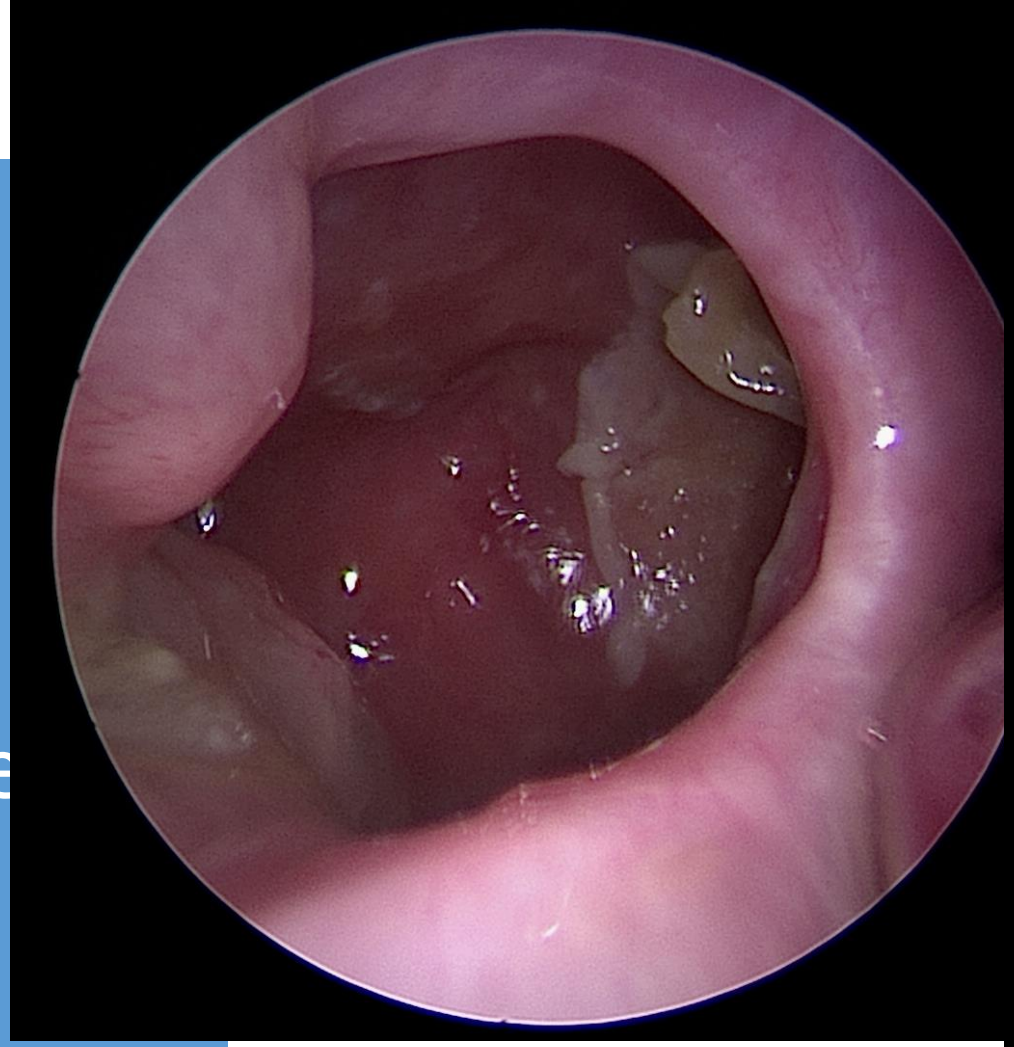
Biggest Current Challenge

1. **Recalcitrant Sinusitis** despite optimum medical and surgical management:
   a. *The altered microbiome (microbial dysbiosis)*

CRSsNP patients…

Biofilm
(Non-Type



Co-morbid Diseases

- When a sinus just does not get better on medical or surgical management…
- **Think outside the box – what else ….**
  - Wegeners, C.F., SLE, Churg-Strauss, Sjogrens, Tumors (Inverting Papillomas), Lymphomas, Foreign Bodies, etc….
- Once ruled out and still ongoing inflammation…

Can we treat CRS by targeting the sinonasal microbiome?

RESEARCH @SPSC

- Dysbiotic microbiome (biofilm formation) of major concern in CRS
- *Could a sinus (snot) microbiota transplant potentially re-set the microbiome!!*

Snot (SNMT) Transplant Study Design: Re-setting the Microbiome…

- Study Design:
  - SNMT vs Placebo
  - 40 patients in each arm.
- … early results

VANCOUVER SUN

UPPING THE COMIC LEVEL
Attell says standup shows are unique B1

BULLYING OFF THE ICE
Coach resigns in protest NP1

THURSDAY, FEBRUARY 7, 2019 SERIOUSLY WESTCOAST SINCE 1912 POSTMEDIA

NEWS

WEATHER
Arctic outflow to dump snow, cold winds A4

END OF ERA
Garage to shut after 87 years A6

Real estate slump to hit tax income

Revenue estimates getting cut by government amid lower sales, prices

JOANNE LEE-YOUNG

The B.C. government is cutting its revenue estimates because of Vancouver's slumping real estate market.

This time last year, Victoria counted in its coffers a record amount in home sale taxes, $260 million more than it had been expecting, thanks to a red hot Metro real estate market.

In mid-February when it releases its 2019 budget, it'll be a different story.

Vancouver homes are languishing on the market for much longer and sales in January were down almost 40 per cent compared the same month in 2018. Prices, especially for higher end homes, have been falling, and in some cases, by significant amounts.

In November, Finance Minister Carole James said the drop in home sales and losses at the Insurance Corp. of B.C. could together mean a $250 million drop in government revenues. To offset this risk, she was increasing a fund to cushion volatile changes by $600 million.

On Wednesday, the Ministry of Finance said in a statement that it has "been carefully monitoring (Metro) housing prices to see how the market responds to our housing actions. In the first and second quarterly reports (April 1 though Sept. 30 of 2018), we lowered our estimate for property tax revenues to reflect the moderation we're seeing."

The province "made a conscious choice" and "it wanted to throw everything it had at the real estate market to have an impact on prices and sales," said Steeve Mongrain, professor of economics at Simon Fraser University, adding that housing taxes account for about nine per cent of B.C. government revenues.

He said government revenues will be harder hit by the drop in the number of home sales that can be taxed than by the drop in the sale prices. Aside from provincial taxes, there have also been measures by municipal and federal governments to cool hot housing markets.

SEE REAL ESTATE ON A2

Dr. Amin Javer treats Maggie Bernet on Wednesday as part of a study at St. Paul's Hospital that will transfer mucus from healthy patients' noses to folks who get repeated sinus infections to see if creating a new microbiome environment will reduce infections. NICK PROCAYLO

NP

HUAWEI
Canada likely to ban firm: experts NP1

Nasal mucus transplants target inflamed sinuses

PAMELA FAYERMAN

There's healthy snot, then there's the other kind. And now those with good nasal mucus will be donating their slimy stuff to relatives suffering from chronically inflamed sinuses in a novel transplantation study at St. Paul's Hospital.

Study leader Dr. Amin Javer said in an interview the inspiration for the chronic rhinosinusitis (CRS) study is the success of fecal transplants for inflammatory bowel diseases and colitis caused by Clos- – has been involved in several human microbiome studies related to the higher risk of hospitalized patients getting potentially deadly C-diff. infections.

Just like what happens in bowel disorders, good microorganisms in the sinus (microbiome) are disrupted and outnumbered by slimy groups of damaging bacterial and/or viral micro-organisms.

Antibiotic therapy is not only often useless but often more damaging since antibiotics cut a wide swath, taking down good bacteria

12 per cent of the North American population.

Indeed, the hospital clinic gets 6,000 outpatient visits a year, many of whom are patients with the chronic sinus condition.

Ethics approval for the St. Paul's Hospital Sino Nasal Microbiota Transplant (SNMT) study, as it is called, has been granted by the hospital and the University of B.C. But Javer is waiting for final approval from Health Canada, which he expects to get next month.

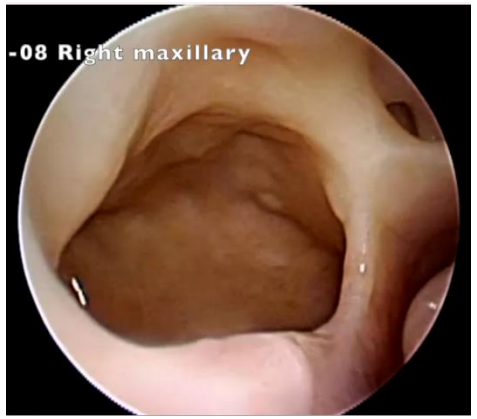
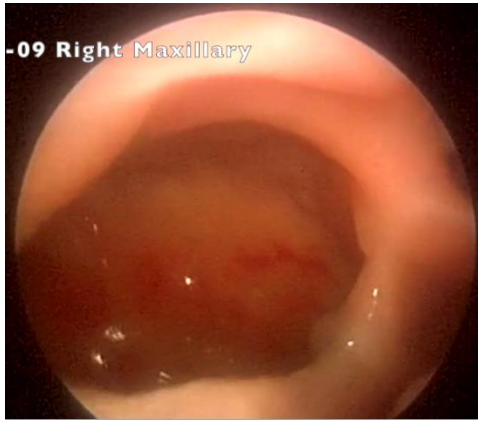
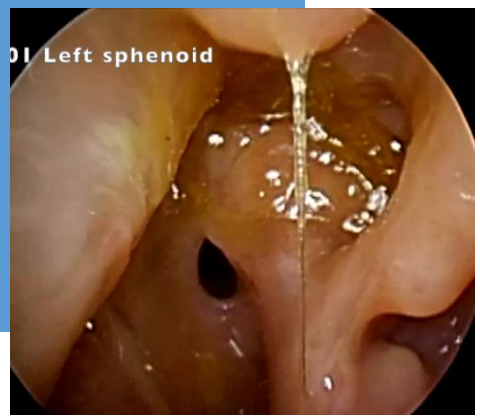
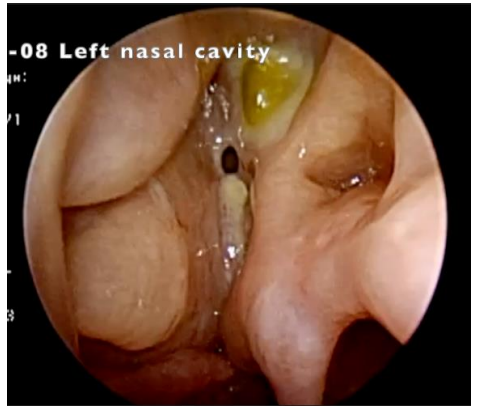
The study aims to answer whether transplants are both beneficial and safe in patients with the chronic condition. The working hypothesis is that inflammation, mucus discharge and recurring infections will indeed be improved by renewing and replenishing the

YOU

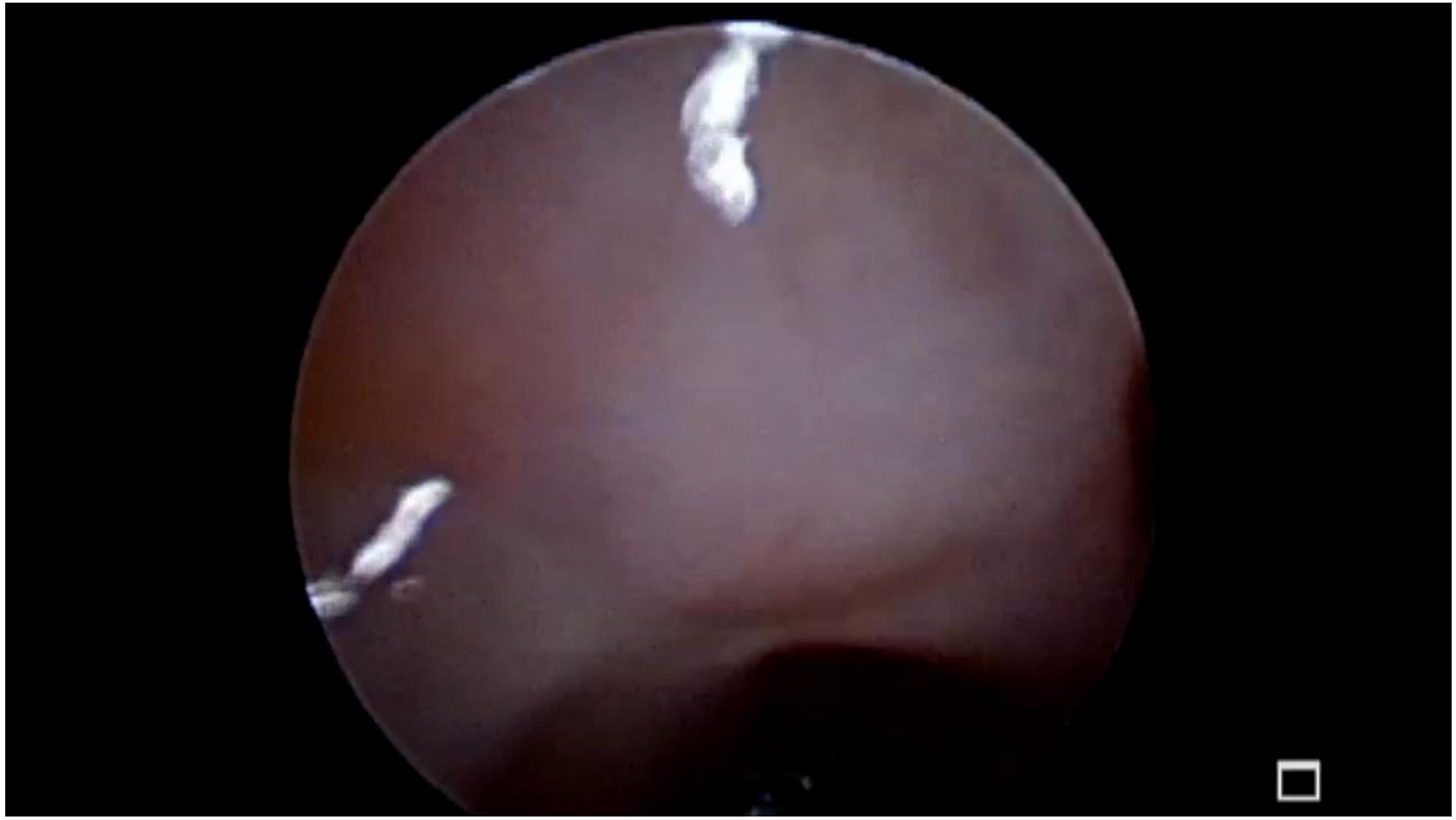
FESTIVAL
New energy at Jewish book event B3

DINING
Dachi keeps it

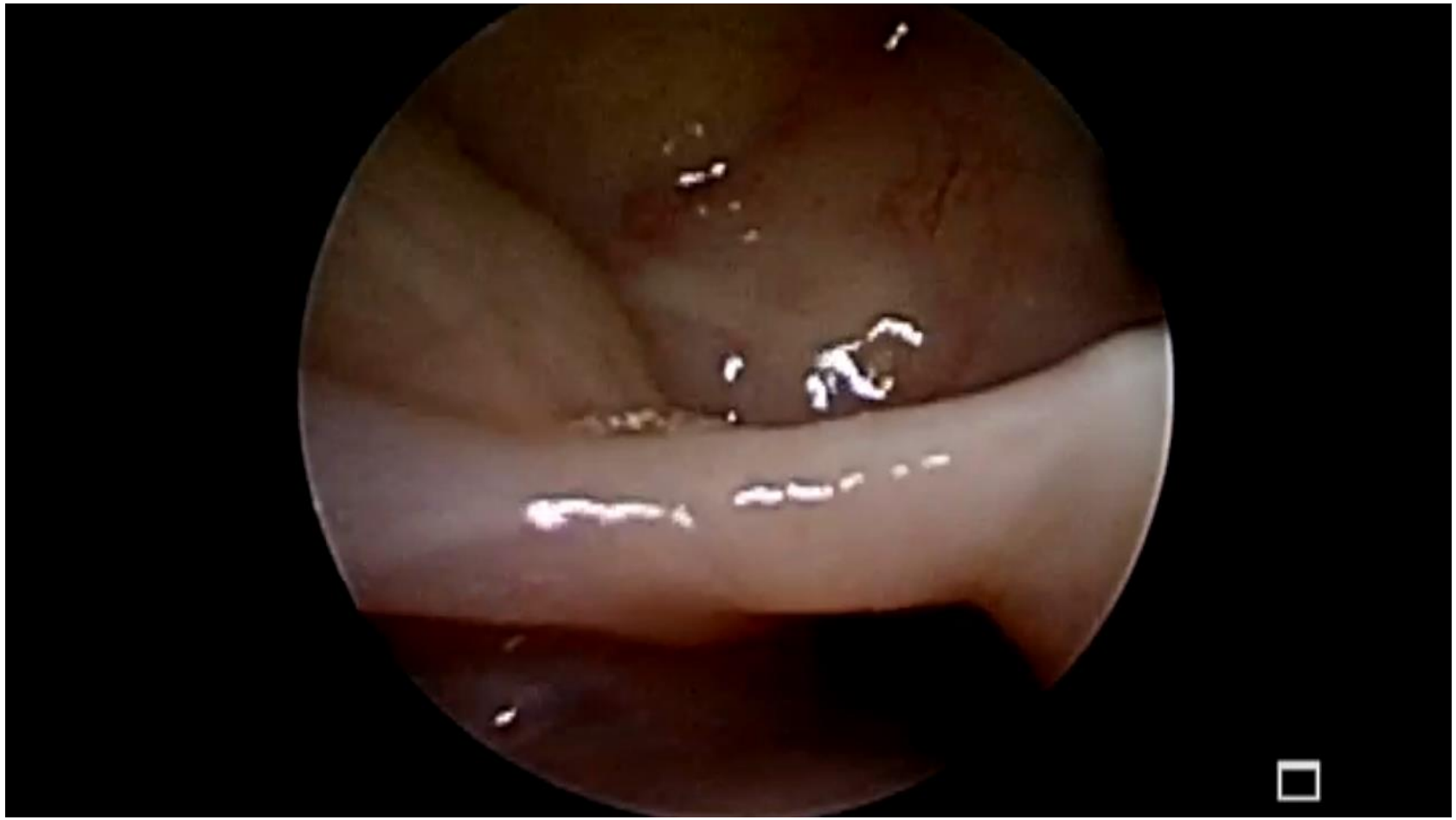
PILOT STUDY RESULTS

	Baseline	Day 30	Day 45	Day 365
Patient 1 SNMT alone	 **SNOT-22 =** 65 pts	 **SNOT-22 =** 0 pts	 **SNOT-22 =** 13 pts	 **SNOT-22 =** 8 pts
Patient 2 aPDT + SNMT	 **SNOT-22 =** 21 pts	 **SNOT-22 =** 15 pts	 **SNOT-22 =** 42 pts	 **SNOT-22 =** 4 pts

Pre-Transplant



Post-Transplant: 6 weeks



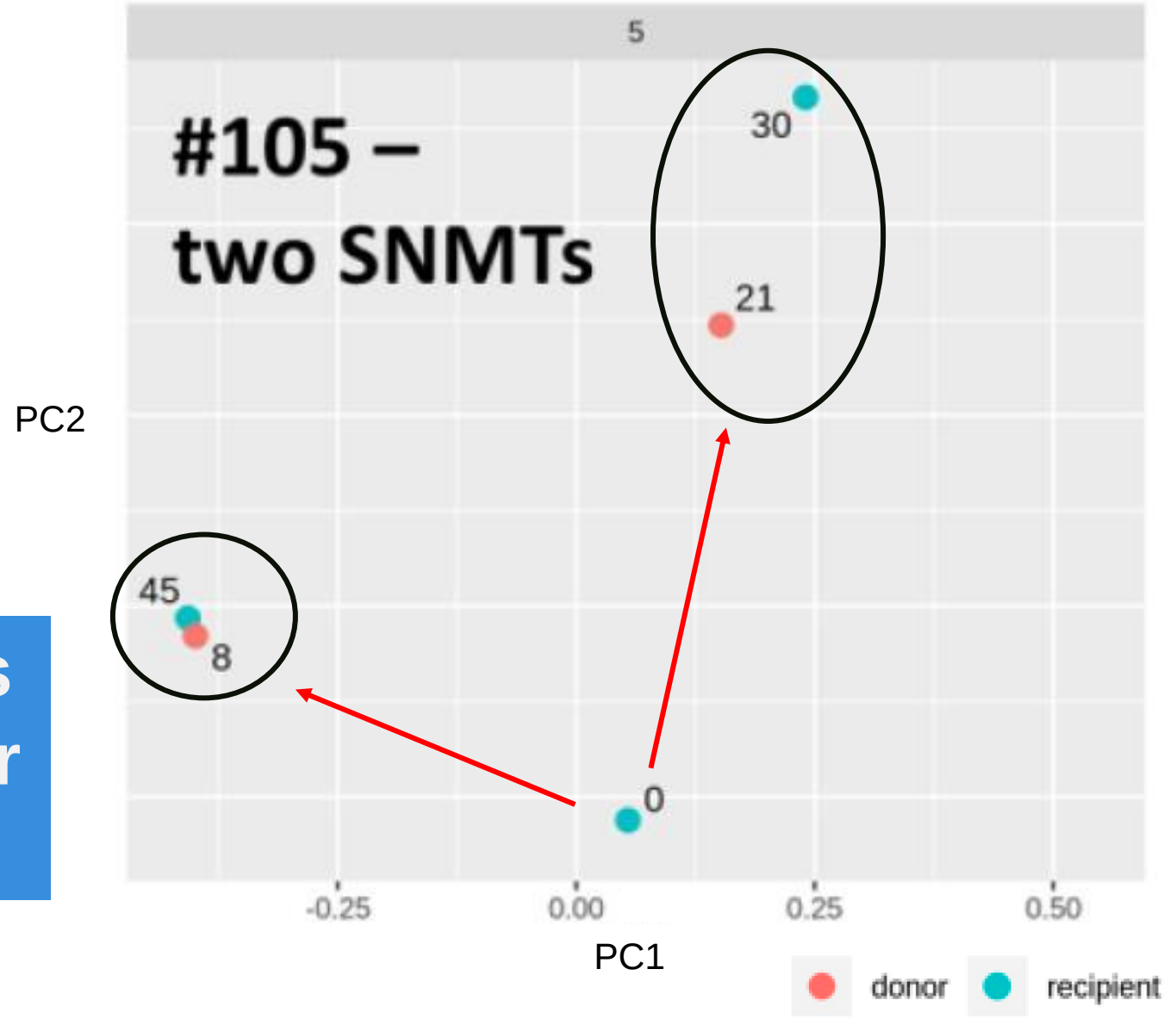
PILOT DATA RESULTS:

PCoA plot showing the microbiome profiles for donor and recipients

Near = similar

Far = different

Recipient becomes similar to the donor after SNMT



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IFAR: International Forum of Allergy & Rhinology

RESEARCH NOTE

SinoNasal Microbiota Transfer to treat recalcitrant chronic rhinosinusitis: A case series

Sandeep K. Gill MSc[1] | Juan C. Hernaiz-Leonardo MD[1,2] | Thaddeus J. Edens PhD[3] | Athenea Pascual PhD[2] | Chris Tang MSc[1] | Judy Fan BSc[2] | Andrew Thamboo MD[2] | Warren Mullings MD[4] | Saad Alsaleh MBBS FRCSC[5] | Bader M. Alim MD[2,6] | Amin R. Javer MD[2] | Amee R. Manges PhD[1,7]

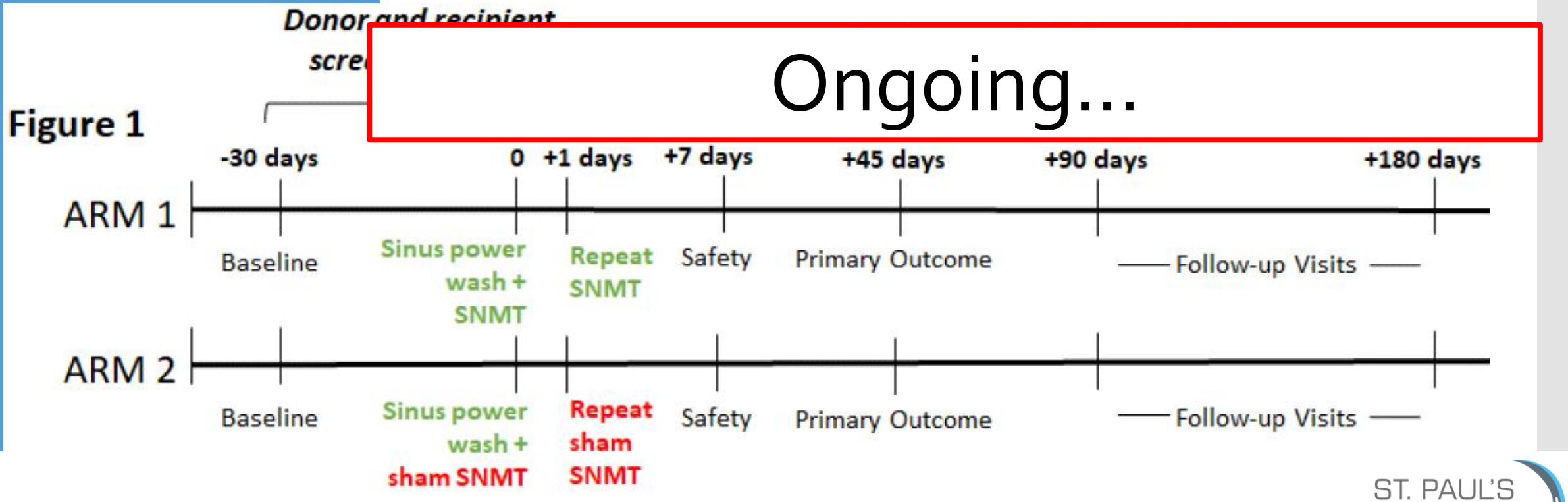
DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

Randomize 80 patents to:

1. **SNMT**
2. **“Sham SNMT” (Placebo)**

CIHR funding

Ongoing...



ST. PAUL'S SINUS CENTRE

SNMT: Mechanistic Studies

IF SNMT works, we want to know WHY it works:

- Does it change the microbiota composition of functional characteristics?

  Whole genome sequencing

Stay tuned for final results…

  Cytokine multiplexing of Sinonasal mucus

- Is SNMT more effective in eosinophilic CRS vs non-eosinophilic CRS?

  Efficacy sub analysis by disease endotype

Thank You