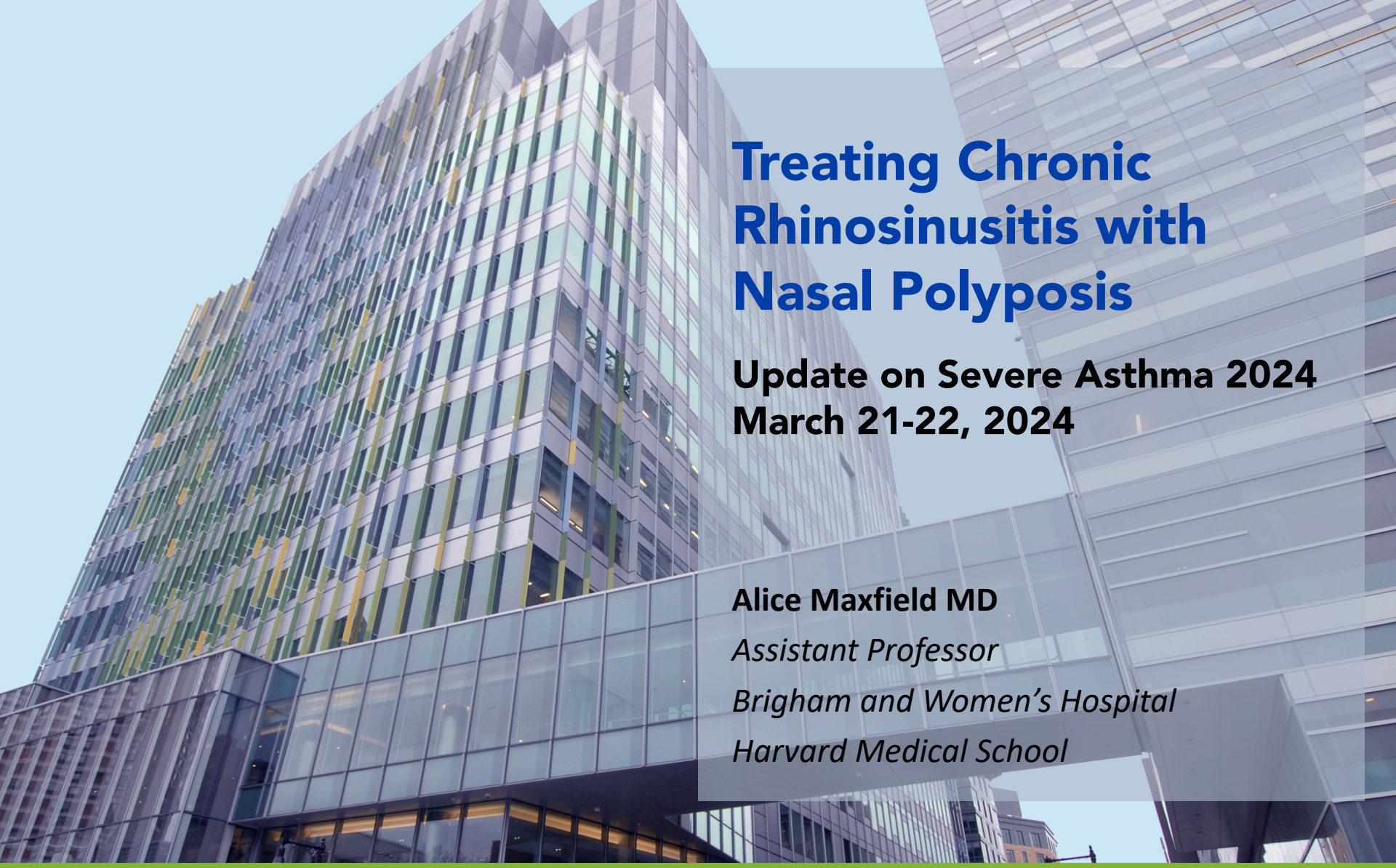


Treating Chronic Rhinosinusitis with Nasal Polyposis

Update on Severe Asthma 2024
March 21-22, 2024

Alice Maxfield MD

Assistant Professor

Brigham and Women's Hospital

Harvard Medical School

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Mass General Brigham

Disclosures

- Alight Care Team
- Vertex

Discuss

- Case example
- Diagnosis of CRS
- Differentiate subtypes of CRS
- Treatment of CRS with nasal polyps

What is Chronic Rhinosinusitis?

Table I-2: Diagnostic criteria for diagnosis of CRS

Greater than or equal to 12 weeks of:

Two or more of the following symptoms:
- Nasal discharge (rhinorrhea or post-nasal drip)
- Nasal obstruction or congestion
- Hyposmia
- Facial pressure or pain
- Cough (in Pediatric CRS)

AND

One or more of the following objective findings:
- Evidence of inflammation on nasal endoscopy or computed tomography
- Evidence of purulence coming from paranasal sinuses or ostiomeatal complex

AND

CRS is divided in to CRSsNP or CRSwNP based on the presence or absence of nasal polyps

ICAR 2020

Case Example

Patient A

- 41yof with sinus issues for the last 2 years
- Started with a cold that never went away
- FESS one year ago
- Persistent facial pressure, thick secretions, PND
- PMH: MS on Rituxan, MGUS, low IgM, prolactinoma

Patient Z

- 27yom with sinus issues for the last few years, worse in the last 6 months
- Feels it may be related to allergies
- Nasal obstruction, congestion, loss of smell
- PMH: seasonal allergies-dust

Patient A

- Cultures: Negative (after abx)
- Allergy testing: skin testing negative
- Asthma: none
- ASA/NSAID: no sensitivity
- SNOT22: 65

Patient Z

- Cultures: none
- Allergy testing: skin testing positive for aspergillus, ragweed, grass, dog, cat, penicillium, birch, oak, dust mites
- Asthma: none
- ASA/NSAID: no sensitivity
- SNOT22: 30

Patient A

- OC/OP: Significant yellow-green purulence along posterior pharyngeal wall, extending from nasopharynx
- Endoscopy exam:
  - Middle meatus w/ significant mucoid drainage
  - Scattered mucoid drainage throughout

Patient Z

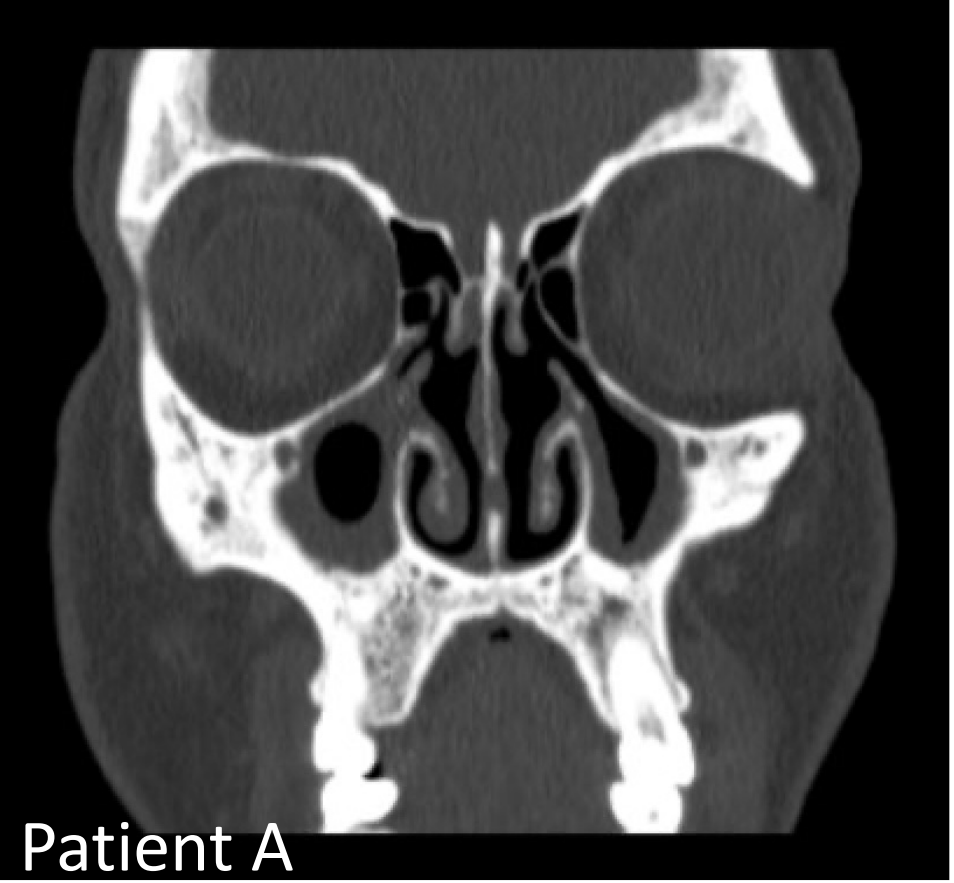
- Voice: hyponasal
- OC/OP: cobblestoning posterior pharynx
- Endoscopy exam:
  - Deviated septum
  - NP extending to floor medial to MT
  - NP full on left, but able to pass the scope

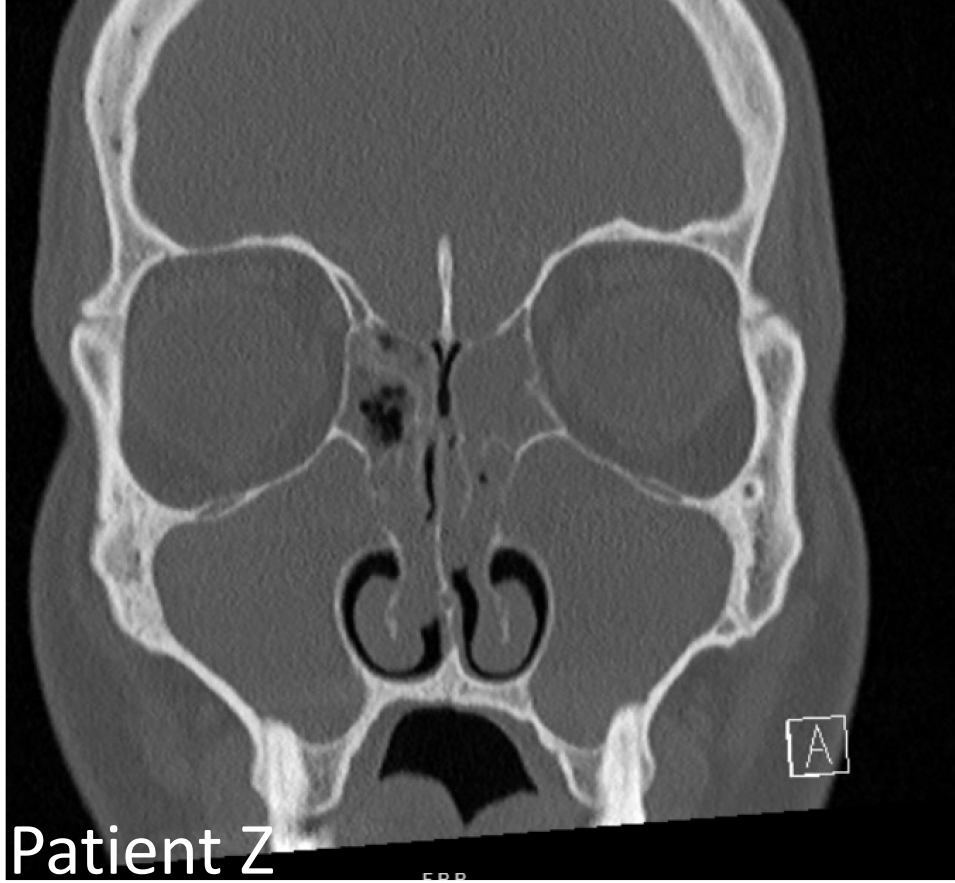
Patient A

- Cultures: Haemophilus influenzae +Beta lactamase

Patient Z

- Cultures: None





CT Imaging

Nasal Polyps on Endoscopy

Patient A

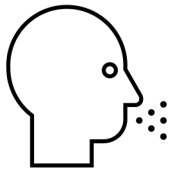
TABLE VII-11. The diagnostic criteria for CRSsNP

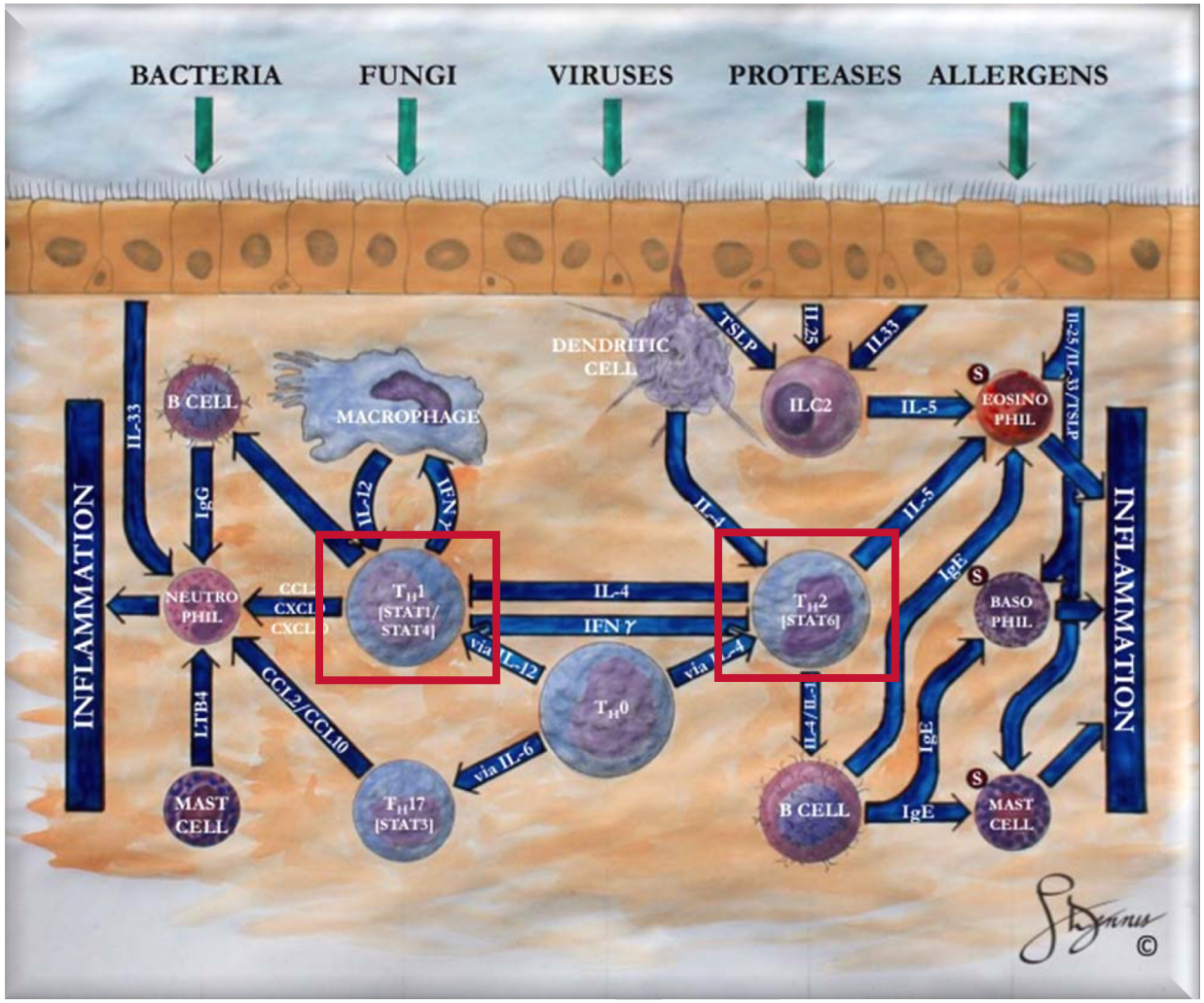
Greater than or equal to 12 weeks of:
2 or more of the following symptoms:
Mucopurulent discharge (rhinorrhea or PND)
Nasal obstruction and congestion
Decreased or absent sense of smell
Facial pressure or pain
AND
1 or more of the following findings:
Evidence of inflammation on paranasal sinus examination or CT
Evidence of purulence coming from paranasal sinuses or OMC
AND
Lack of polyps

Patient Z

TABLE VIII-6. The diagnostic criteria for CRSwNP

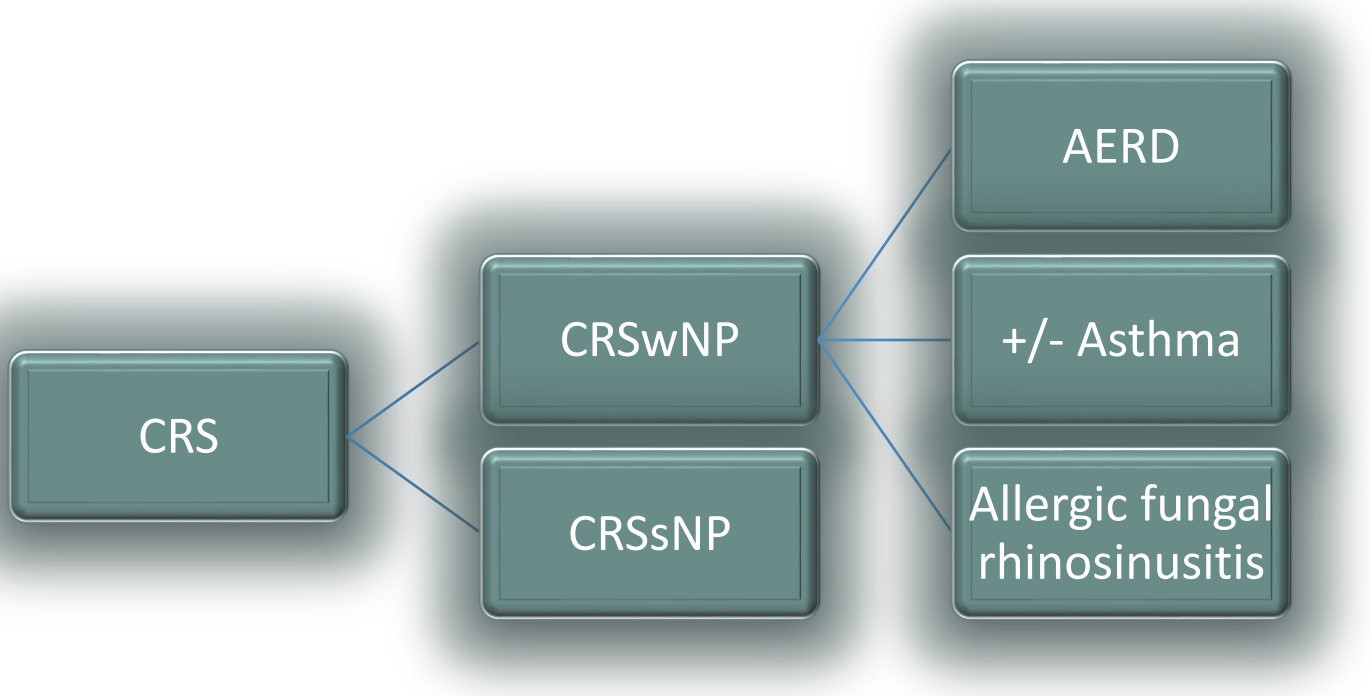
Greater than or equal to 12 weeks of:
2 or more of the following symptoms:
Mucopurulent discharge (rhinorrhea or PND)
Nasal obstruction and congestion
Decreased or absent sense of smell
Facial pressure or pain
AND
1 or more of the following findings:
Evidence of inflammation on paranasal sinus examination or CT
Evidence of purulence coming from paranasal sinuses or ostiomeatal complex
AND
Presence of polyps





Dennis et al. 2016.

What is the difference between the phenotypes of CRS?



Original Research—Sinonasal Disorders

Periostin as a Biomarker for Nasal Polyps in Chronic Rhinosinusitis

Alice Z. Maxfield, MD[1,2], Lukas D. Landegger, MD[2,3], Christopher D. Brook, MD[4], Ashton E. Lehmann, MD[2,3], Adam P. Campbell, MD[2,3], Regan W. Bergmark, MD[2,3], Konstantina M. Stankovic, MD, PhD[2,3]*, and Ralph Metson, MD[2,3]*

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
2018, Vol. 158(1) 181–186

DOI: 10.1177/0194599817737967
http://otojournal.org
SAGE

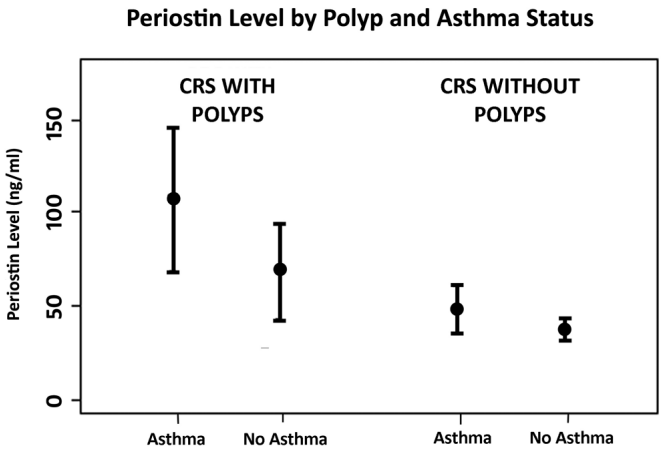


Figure 2. Periostin levels by nasal polyp and asthma status. Although mean serum periostin levels were higher for patients with asthma in both groups—chronic rhinosinusitis (CRS) with and without nasal polyps—this difference was not significant. Values are presented as means (95% CI).

Original Research—Sinonasal Disorders

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
2018, Vol. 158(1) 181–186

DOI: 10.1177/0194599817737967
http://otojournal.org
SAGE

Periostin as a Biomarker for Nasal Polyps in Chronic Rhinosinusitis

Alice Z. Maxfield, MD[1,2], Lukas D. Landegger, MD[2,3], Christopher D. Brook, MD[4], Ashton E. Lehmann, MD[2,3], Adam P. Campbell, MD[2,3], Regan W. Bergmark, MD[2,3], Konstantina M. Stankovic, MD, PhD[2,3]*, and Ralph Metson, MD[2,3]*

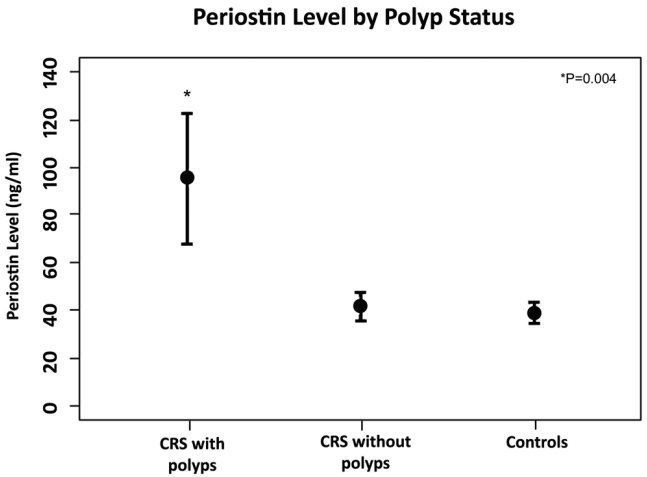


Figure 1. Periostin level by nasal polyp status. Serum periostin level was significantly higher in patients with chronic rhinosinusitis (CRS) and nasal polyps versus patients with CRS without nasal polyps and controls (P = .004). Values are presented as means (95% CI).

Goals of treatment

- Increase quality of life
- Control disease progression

- Enhance mucociliary clearance
- Improving sinus drainage pathways
- Eradicate local infection/inflammation
- Improve access for delivery of topical medications

Challenges in Treatment of CRS

- Difficulty correlating patient symptoms with objective measures of inflammation
- Predicting long term response to medical therapy
- Relapses of symptoms and disease

ORIGINAL ARTICLE

International Consensus Statement on Allergy and Rhinology: Rhinosinusitis

CRSwNP Treatment

- Nasal saline irrigation
- Topical steroids
- Oral corticosteroids (A)
- Antibiotics
  - Oral
  - Irrigation (A) [CRSwNP and CRSsNP]
- ASA desensitization for AERD (A)
- Dupilumab (A)
- Endoscopic Sinus Surgery

CRSwNP Treatment

- Nasal saline irrigation (No studies)
- Topical steroids
  - Spray (A, strong recommendation)
  - Irrigation (ie budesonide) (A, strong recommendation)
- Oral corticosteroids (A)
- Antibiotics
  - Oral
    - Nonmacrolide <3 weeks (B)
    - Nonmacrolide >3 weeks (N/A)
    - Macrolide (B)
  - Irrigation (A) [CRSwNP and CRSsNP]
- ASA desensitization for AERD (A)
- Dupilumab (A)
- Endoscopic sinus surgery

Hopkins et al. 2015
Benninger et al 2016

Nasal Saline Irrigation

- Isotonic saline irrigation
- Low positive pressure
- Used in combination with intranasal corticosteroid spray
- RCT showed improved symptom severity, symptom frequency, QOL
- Benefits:
  - Mucociliary clearance
  - Clear eosinophilic mucin
  - Decreased viscosity
  - Decreased edema
  - Mechanical lavage of debris
  - Decreased medication usage, specifically antibiotics

Pynnonen et al. 2007

Topical Intranasal Corticosteroids (A, strong recommendation)

- Improvement:
  - sinonasal symptoms – nasal blockage, rhinorrhea, smell
    (not for facial pressure/pain)
  - polyp size and recurrence
  - QOL
  - olfaction
- Especially when used in combination with nasal saline irrigation.
- No difference in effectiveness between types of intranasal steroids.

Fokkens et al. 2012
Orlandi et al. 2016
Chong et al. 2016
Kalish et al. 2012

Topical Mometasone Irrigation

- Dilute irrigation: 240mL of saline with 2mg of mometasone 1-2x daily
- Low concentration 0.6 mg vs high concentration 2-4mg
- Superior pharmacokinetic profile, increased local efficacy, low systemic absorption
- Mometasone 2mg daily via nasal spray or large volume irrigation for 12 months
  - The irrigation group had larger improvement in nasal blockage, LM Score, and modified LK score.
  - Overall 12 month symptom VAS was better in the irrigation group.
- Corticosteroid irrigation is beneficial in long term maintenance in CRSwNP, and f/u longer than 3-6 months post ESS.
- In CRSwNP, no evidence of HPA axis suppression with mometasone irrigation (2mg twice daily).

Brown et al. 2021
Harvey et al. 2018
Talat et al. 2021

Oral Corticosteroids

(A, strong recommendation for short-term use)

- Short term improvement in sinonasal symptoms
- No long-term improvement
- Need to weigh risks and benefits/adverse effects

Oral Non-Macrolide Antibiotics
(B, recommendation against)

- Lack of good data regarding efficacy
- Some studies show benefit in patients with polyps
- Cochrane review – very little evidence that systemic antibiotics are effective in patients with CRS
- More studies needed in the subtypes of CRS
- Short course doxycycline appears to have some benefit in those with nasal polyp

- Long term macrolides have mixed results, no clear lasting benefit.

Barshak & Durand 2017

The Laryngoscope

General Antibiotic Exposure Is Associated With Increased Risk of Developing Chronic Rhinosinusitis

Alice Z. Maxfield, MD; Hakan Korkmaz, MD; Luciano L. Gregorio, MD; Nicolas Y. Busaba, MD; Stacey T. Gray, MD; Eric H. Holbrook, MD; Rong Guo, MS; Benjamin S. Bleier, MD

Oral Macrolide Antibiotics
(B, option)

- Macrolide antibiotics have anti-inflammatory and immunomodulatory properties
- There is an effect on the neutrophilic components of the inflammatory response, thereby targeting Th1-mediated non eosinophilic CRS.

Barshak & Durand 2017

ASA Desensitization in AERD
(A, recommendation)

- Improvement in
  - HRQoL
  - Sinusitis symptoms
  - Smell
  - Rescue nasal polyp surgery
  - Nasal polyp size
- Lasting endoscopic and symptomatic improvement

Oykhman et al. 2021

Endoscopic Sinus Surgery

Mucosal preserving

Widen sinus drainage pathways

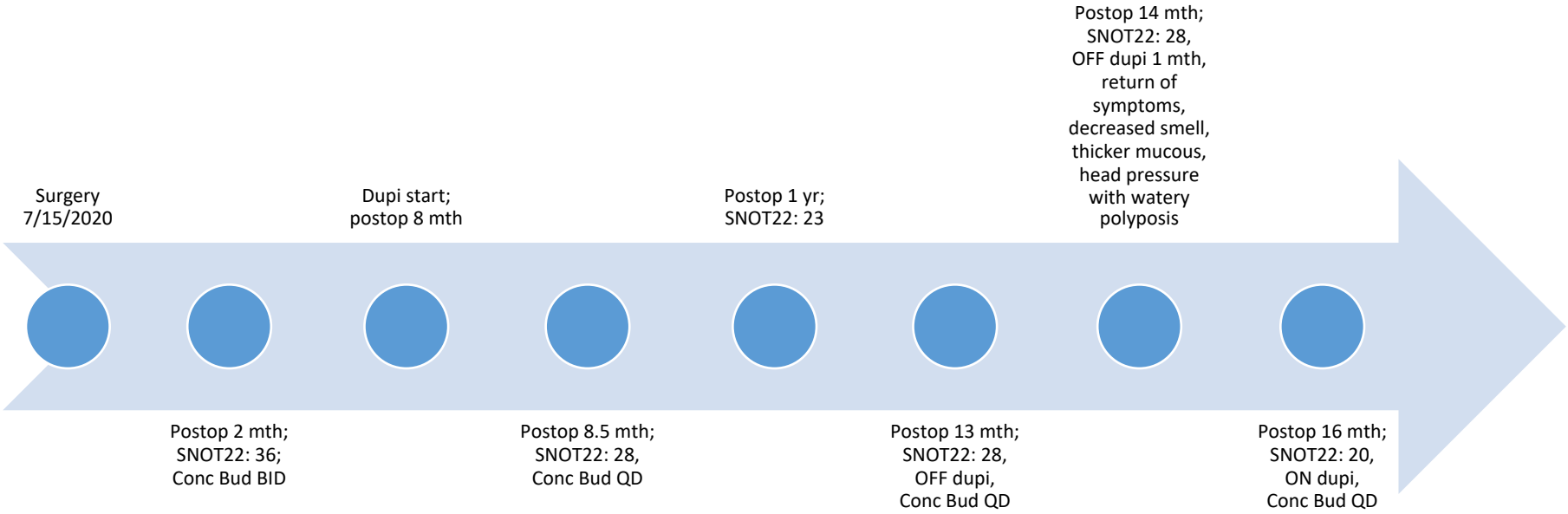
Allow better delivery of medication

Establish nasal airway and sinus outflow

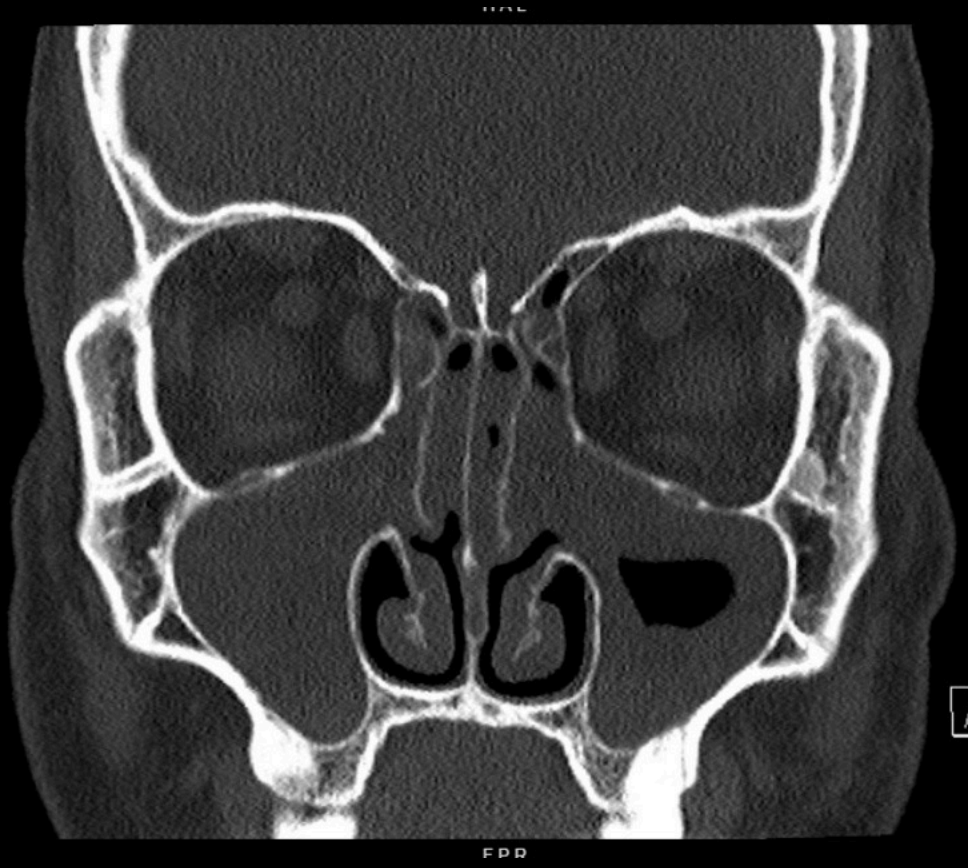
Decrease overall inflammatory disease burden

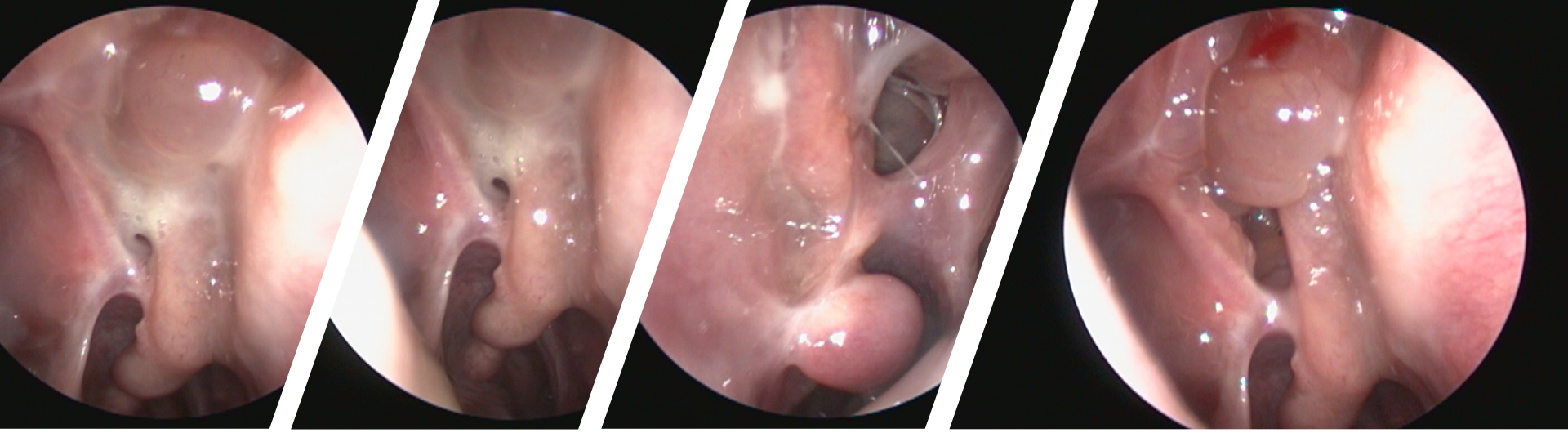
CRSwNP s/p surgery, budesonide dilute

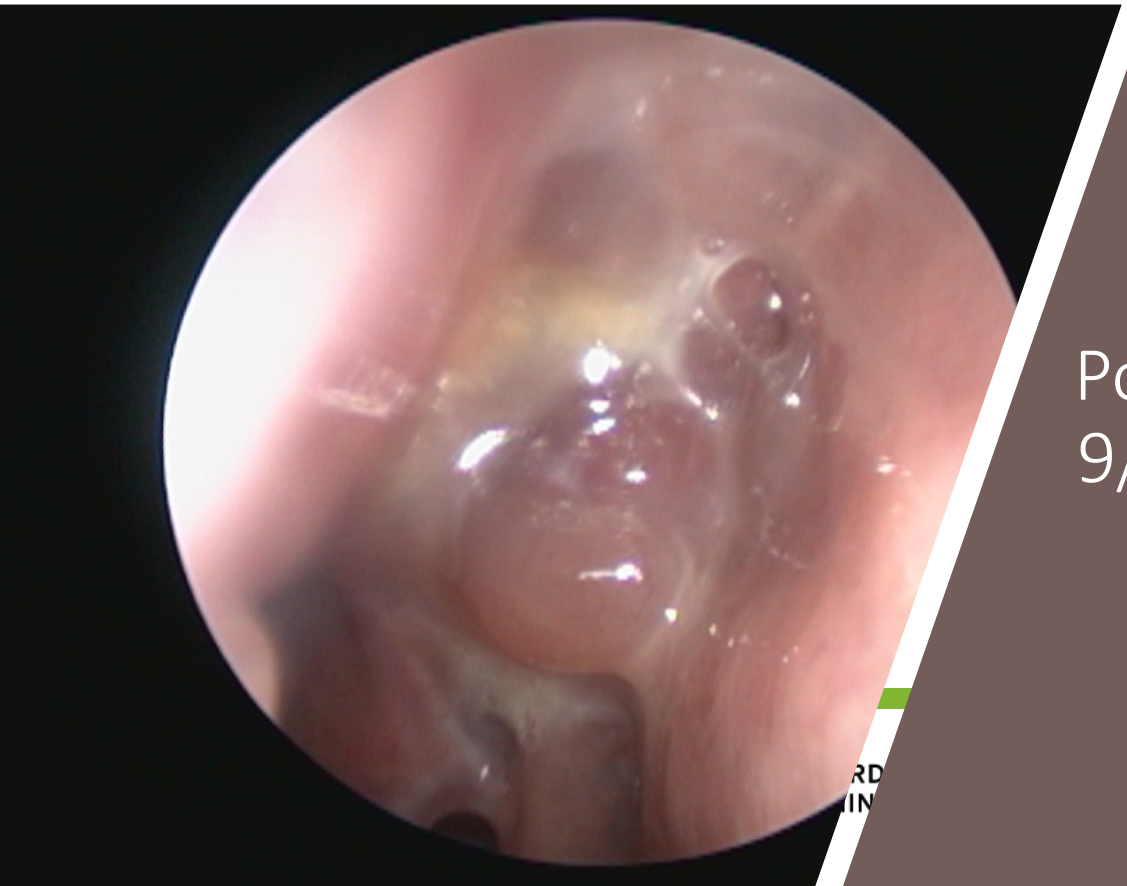
Patient RR


Surgery
7/15/2020
Postop 2 mth;
SNOT22: 36;
Conc Bud BID
Dupi start;
postop 8 mth
Postop 8.5 mth;
SNOT22: 28,
Conc Bud QD
Postop 1 yr;
SNOT22: 23
Postop 13 mth;
SNOT22: 28,
OFF dupi,
Conc Bud QD
Postop 14 mth;
SNOT22: 28,
OFF dupi 1 mth,
return of
symptoms,
decreased smell,
thicker mucous,
head pressure
with watery
polyposis
Postop 16 mth;
SNOT22: 20,
ON dupi,
Conc Bud QD

Preoperative



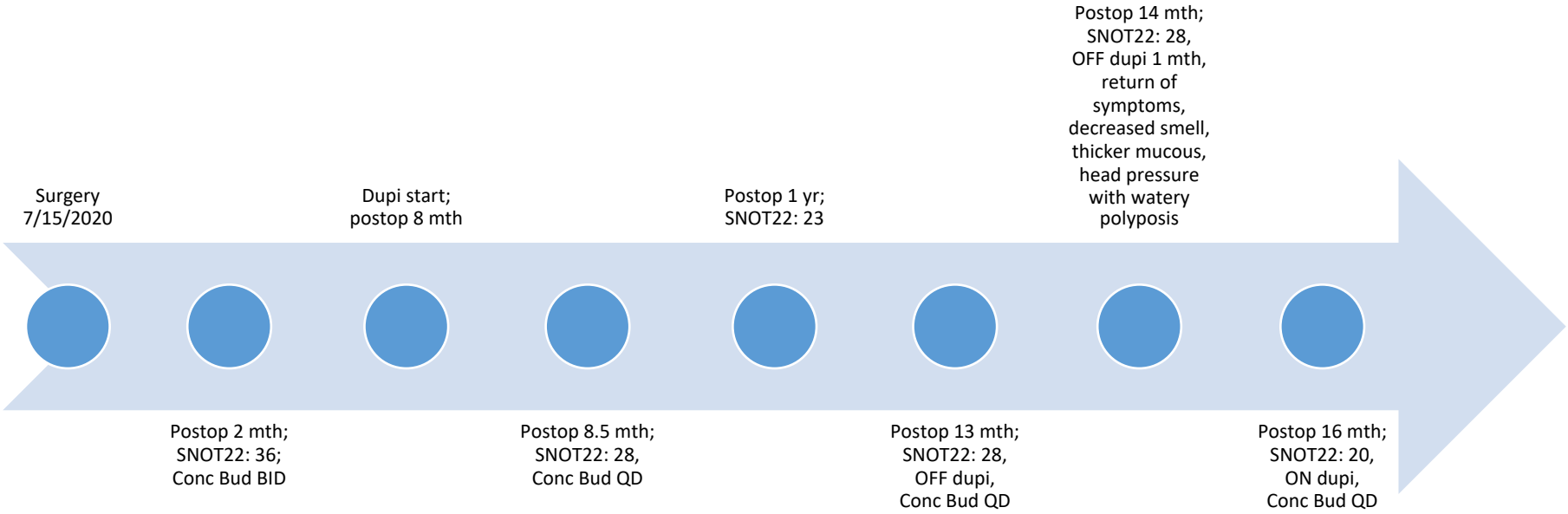




Postoperative 2 months 9/25/2020: SNOT22 39, conc budesonide BID

ON dupilumab for 5 mths, OFF for 1 mth

Patient RR


Surgery
7/15/2020
Postop 2 mth;
SNOT22: 36;
Conc Bud BID
Dupi start;
postop 8 mth
Postop 8.5 mth;
SNOT22: 28,
Conc Bud QD
Postop 1 yr;
SNOT22: 23
Postop 13 mth;
SNOT22: 28,
OFF dupi,
Conc Bud QD
Postop 14 mth;
SNOT22: 28,
OFF dupi 1 mth,
return of
symptoms,
decreased smell,
thicker mucous,
head pressure
with watery
polyposis
Postop 16 mth;
SNOT22: 20,
ON dupi,
Conc Bud QD

Biologics

REVIEW ARTICLE

The role of biologics in chronic rhinosinusitis: a systematic review

Isma Z. Iqbal, PgCertMEd, FRCS(ORL-HNS)[1], Stephen Shih-Teng Kao, MBBS, MClinSc[2] and Eng Hooi Ooi, PhD, FRACS[3]

Table 1 Table Describing Biologics Discussed Including: Name, Target, FDA Approvals, Mechanism, Dosing and Side Effects

Generic Name	Trade Name	Target	FDA Approvals	Dosing	Side Effects
Omalizumab	Xolair	Anti-IgE via Fc receptor blockade	CRSwNP; Allergic Asthma; Chronic Uticaria	Subcutaneous injection every 2–4 weeks	• Sinusitis • Headache • Pharyngitis • Injection site reaction • 0.2% risk of anaphylaxis
Mepolizumab	Nucala	Anti-IL5	Eosinophilic Asthma	Monthly subcutaneous injections	• Headache • Fatigue • Injection site reaction
Benralizumab	Fasenra	Anti-IL5 via IL5-R alpha receptor blockade		Monthly subcutaneous injections for 3 months then every other month	• Headache • Pharyngitis • Injection site reaction
Dupilumab	Dupixent	Anti-IL4 and IL-13 via IL-4Ra receptor blockade	CRSwNP; Atopic Dermatitis	Subcutaneous injection every other week	• Nasopharyngitis • Headache • Injection site reaction

Anti-IL33

Tezepelumab (Tezspire) - Anti-TSLP

Morse, Miller, Senior. 2021

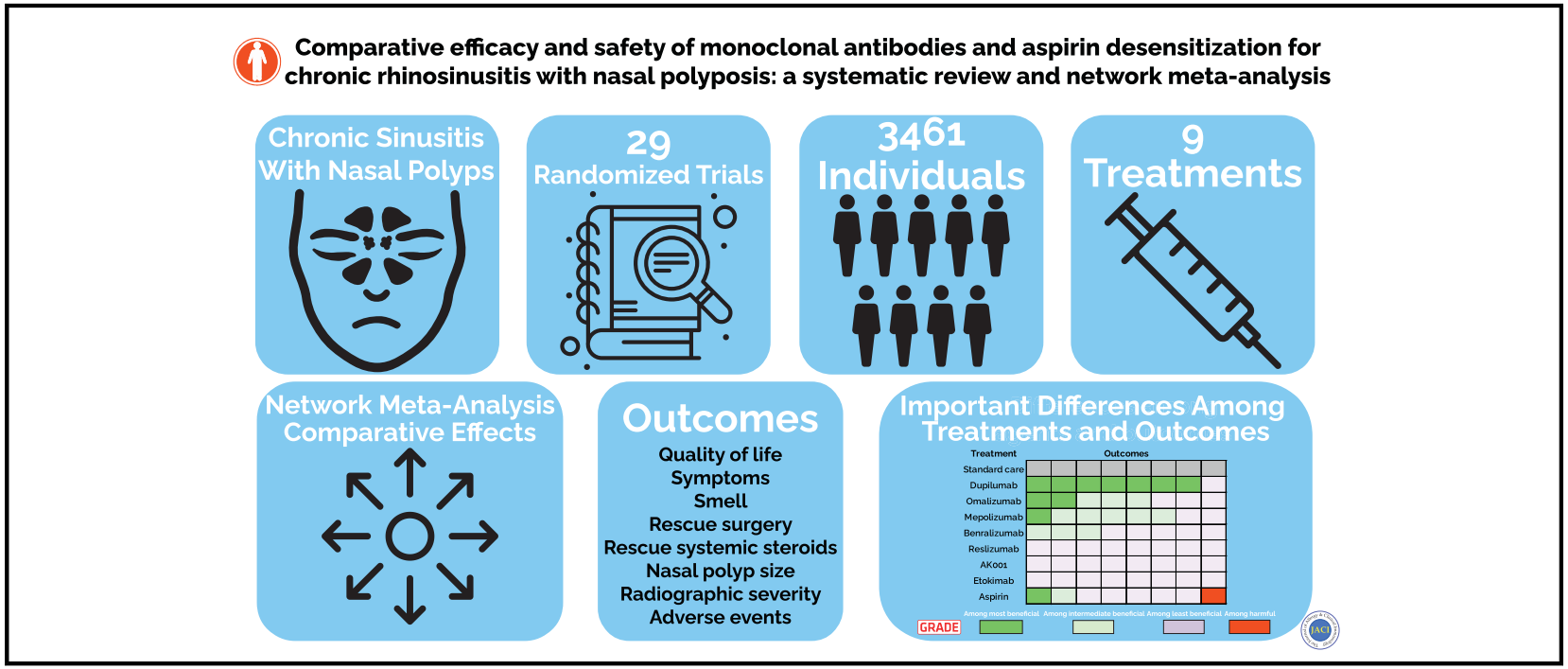
Biologics for Nasal Polyposis

- Cost
  - Estimated cost per year >$30,000 on average
  - Cost utility analysis of dupilumab vs ESS
    - Surgery cost $50,346.99 with 9.80 QALYs vs. dupilumab cost $536,420.22 with 8.95QALYs
    - Authors concluded that ESS was less costly and more effective than dupilumab.

(Scangas et al)

Paul Oykhman, MD, MSc,[a] Fernando Aleman Paramo, MD,[a] Jean Bousquet, MD,[d,e,f] David W. Kennedy, MD,[g] Romina Brignardello-Petersen, PhD,[b] and Derek K. Chu, MD, PhD[a,b,c] *Hamilton, Ontario, Canada; Berlin, Germany; Montpellier, France; and Philadelphia, Pa*

GRAPHICAL ABSTRACT



	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	**-19.91** (-22.50, -17.32)	**-3.25** (-4.31, -2.18)	**10.96** (9.75, 12.17)	**-21.73** (-24.61, -18.22) RR 0.32 (0.23, 0.43)	**-16.35** (-18.13, -13.48) RR 0.22 (0.14, 0.36)	**0.13** (-8.12, 9.88) RR 1.00 (0.88, 1.13)	**-2.04** (-2.73, -1.35)	**-7.51** (-10.13, -4.89)
Omalizumab	**-16.09** (-19.88, -12.30)	**-2.09** (-3.15, -1.03)	**3.75** (2.14, 5.35)	**-12.46** (-23.65, 12.78) RR 0.61 (0.26, 1.40)	**-7.40** (-11.04, -2.43) RR 0.65 (0.48, 0.88)	**-2.60** (-15.58, 13.28) RR 0.96 (0.79, 1.18)	**-1.09** (-1.70, -0.49)	**-2.66** (-5.70, 0.37)
Mepolizumab	**-12.89** (-16.58, -9.19)	**-1.82** (-3.13, -0.50)	**6.13** (4.07, 8.19)	**-10.23** (-15.98, -2.88) RR 0.68 (0.50, 0.91)	**-12.33** (-15.56, -7.22) RR 0.41 (0.26, 0.66)	**-3.07** (-13.44, 9.07) RR 0.96 (0.82, 1.12)	**-1.06** (-1.79, -0.34)	
Benralizumab	**-7.68** (-12.09, -3.27)	**-1.15** (-2.47, 0.17)	**2.95** (1.02, 4.88)	**-9.91** (-16.30, -0.96) RR 0.69 (0.49, 0.97)	**-2.53** (-9.05, 7.16) RR 0.88 (0.57, 1.34)	**-1.48** (-13.28, 12.54) RR 0.98 (0.82, 1.17)	**-0.64** (-1.39, 0.12)	**-1.00** (-3.83, 1.83)
Reslizumab					**-18.82** (-20.93, 20.56) RR 0.11 (0.01, 1.98)	**-2.55** (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						**2.54** (-27.11, 51.03) RR 1.03 (0.63, 1.69)	**-0.20** (-1.61, 1.21)	
Etokimab	**-1.30** (-8.99 to 6.40)					**188.14** (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	**-0.33** (-1.58, 0.92)	
ASA Desensitization	**-10.61** (-14.51, -6.71)	**-2.74** (-3.92, -1.57)	**2.72** (-1.17, 6.61)		**-16.00** (-19.79, 0.21) RR 0.24 (0.06, 1.01)	**209.21** (8.30, 901.87) RR 3.84 (1.11, 13.22)	**-0.95** (-2.44, 0.55)	**-0.31** (-3.50, 2.88)

Classification of intervention (colour)[24]				**Certainty (shading)[24, 29]**
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

American Journal of Otolaryngology–Head and Neck Medicine and Surgery 43 (2022) 103615

Contents lists available at ScienceDirect

American Journal of Otolaryngology–Head and Neck Medicine and Surgery

journal homepage: www.elsevier.com/locate/amjoto

Adverse events of biological therapy in chronic rhinosinusitis with nasal polyps: A systematic review

Ahmad Aldajani [a,b,*], Ahmad Alroqi [b,1,2], Saud Alromaih [b,2], Mohammad O. Aloulah [b,2], Saad Alsaleh [b,2]

Grouped total number of complication and the frequency of the commonest adverse events per each drug.

Drug	Number of studies	Size	Complications							
			Total (n)	Asthma (%)	Epistaxis (%)	Headache (%)	Erythema/ allergy (%)	Nasal polyps/congestion/ pharyngitis/infections (%)	Serious	Death
Dupilumab	6	1003	818	18 (1.7 %)	52 (5.1 %)	82 (8.1 %)	95 (9.4 %)	225 (22.4 %)	36	0
Omalizumab	3	157	202	5 (3.1 %)	4 (2.5 %)	15 (9.5 %)	8 (5 %)	34 (21.6 %)	3	0
Mepolizumab	3	90	76	2 (2.2 %)	1 (1.1 %)	14 (15.5 %)	–	36 (40 %)	1	0
Reslizumab	1	78	28	–	–	–	–	28 (35.8 %)	–	–

CME Review

A call for cost-effectiveness analysis for biologic therapies in chronic rhinosinusitis with nasal polyps

Christopher D. Codispoti, MD, PhD; Mahboobeh Mahdavinia, MD, PhD

Rush University, Chicago, Illinois

Unanswered questions

- Which type of patient?
  - Refractory disease
- Timing of biologic?
- Is there a clear advantage of biologic over surgery?
  - Durability of surgery is improved compared to dupilumab.
- Is there advantage between biologics?
  - Current FDA approval and trial data suggests dupilumab is most efficacious choice in Caucasian populations with CRSwNP.
- Long term results?
- Long term side effects?

Morse, Miller, Senior. 2021

Maximal Medical Therapy?

- There is no standardized medical therapy regimen for CRS.
- Lal et al. treated with minimum 4 weeks -
  oral antibiotics, oral steroids, topical nasal steroids, topical nasal decongestant rotation, saline irrigation
  - 51% successfully treated
  - 17% partial improvement
  - 31% underwent surgery

Lal et al. 2014.

- Mucosal preserving
- Widen sinus drainage pathways
- Allow better delivery of medication
- Establish nasal airway and sinus outflow
- Decrease overall inflammatory disease burden

Endotyping

- CRS currently classified by phenotype.
- 38-51% of CRS patients fail to respond to recommended medical therapies.
- This highlights the limitations of the current treatments of CRS.
- There is heterogeneity within cellular and molecular pathways that lead to these subtypes.
- Thus, defining molecular biomarkers to further endotype these subtypes is crucial in determining targeted therapies.

Lal et al. 2016.
Baguley et al. 2014

Summary

- CRSwNP is a type II mediated inflammatory process.
- Asthma and CRS are highly associated and consideration of both is necessary for optimizing treatment.
- Nasal saline irrigation with corticosteroid spray is the first line and has been found to be useful.

Summary

- It is important to delineate the subtypes of CRSwNP to determine best treatment.
- Endotyping with molecular biomarkers is important for future advancements to better classify CRS patients and allow for tailored therapies.

Thank you!