

Aspirin-Exacerbated Respiratory Disease – Bridging History, Science, and Patient Care

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BRIGHAM AND
WOMEN'S HOSPITAL
| **AERD Center** |



Laidlaw Lab

RESPIRATORY INFLAMMATION
investigate . discover . treat



HARVARD
MEDICAL SCHOOL

Learning Objectives

Upon completion of this learning activity, participants should be able to:

- Describe the clinical presentation of patients with AERD, including the classical triad, and how some patients may present with symptoms outside of that classical triad.
- Describe the application of current medical best practices for the diagnosis and treatment of patients with AERD.
- Summarize the evidence for the use of currently-available biologics in AERD.

Overview of slides



Brief history lesson on AERD



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Findings from our cohort at BWH AERD Center



NSAID reactions – aspirin challenges & desensitization

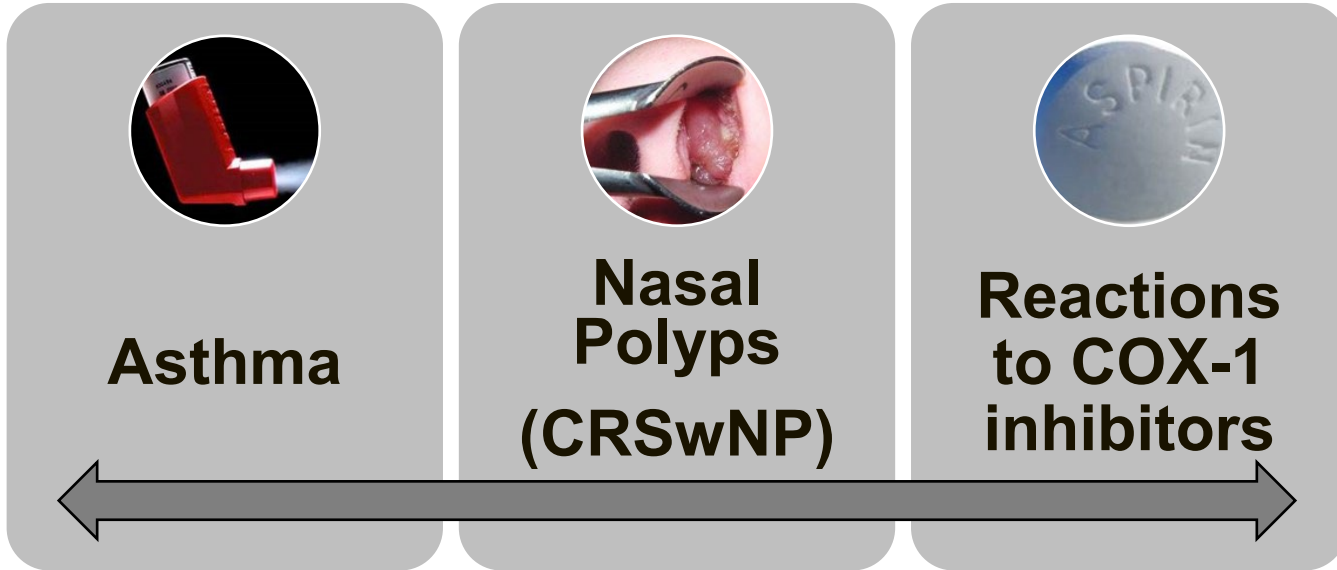


Mechanism & biologics

**FOOD
&
WINE**

Alcohol & diet

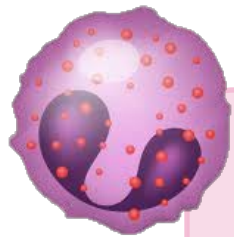
AERD presents (usually) in adulthood, with a stereotyped pattern and common phenotype



How common is it?

- 7% of adults with asthma
- 14% of adults with severe asthma
- 25% of adults with asthma + polyps

Rajan and White, et al. JACI 2015, Meta-analysis



**Eosinophils
in tissues
and blood**



**Sinus
disease
is severe**

**Anosmia,
polyp
recurrence**

Nomenclature

Brief history lesson, 1922



Figure 1. Georges Fernand Isidore Widal (1862–1929).

Widal F, Abrami P, Lermoyez J: Anaphylaxie et idiosyncrasie. Presse Medicale 30:189- 193,1922

“**Madame M.**” → symptoms began at 27yo, rash, swelling, paroxysmal attacks of runny nose and congestion, nighttime asthma attacks, ‘mucous rhinopharyngeal polyps’ removed multiple times (grew back every time!), and then systemic reactions to aspirin and antipyrine.

Successful desensitization to aspirin up to 600mg (took several weeks), with cross-desensitization to antipyrine.

“Indeed, despite the considerable difference that exists in their chemical structure, we were very surprised to note that the desensitization to aspirin had also resulted, at the same time, in a desensitization against antipyrine”

Brief history lesson, 1968

ANNALS OF INTERNAL MEDICINE

Volume 68

May 1968

Number 5

Intolerance to Aspirin

Clinical Studies and Consideration of its Pathogenesis

MAX SAMTER, M.D., F.A.C.P., and RAY F. BEERS, JR., M.D.
Chicago, Illinois



TABLE 1. Clinical Features of 182 Aspirin-Sensitive Patients

Data	No. of Patients
Sex: male	78
female	104
Onset before age 30	46
Duration of aspirin sensitivity:	
less than 5 years	70
more than 5 years	112
Respiratory symptoms only	154
Angioneurotic edema and urticaria only	18
Respiratory symptoms and urticaria	10
Family history of atopy	40
Positive skin reactions to seasonal and environmental inhalant allergens	19
Nasal and paranasal polyps	92
Polypectomies	72
First attack of bronchial asthma within 9 months after polypectomy	18
Bronchial asthma aggravated by polypectomy	30
Associated sensitivities	42*

Brief history lesson, 1968

ANNALS OF INTERNAL MEDICINE

a few of our patients (16 of 182) have become free of asthma unless attacks are precipitated by aspirin. It is interesting, however, that no patient under our care has ceased to form nasal polyps once the presence of polyps had been established.

Number 5
genesis



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The onset of the reaction is marked by profuse watery rhinorrhea and, often, by a vivid scarlet flush of head, neck, upper chest, and extremities. At times, the initial reaction is followed by nausea, vomiting, intestinal cramps, and diarrhea. Bronchoconstriction, wheezing (without impressive cough), and cyanosis occur, as a rule, within a few minutes after the nasal symptoms.

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Brief history lesson, 1984

Aspirin-sensitive rhinosinusitis asthma: A double-blind crossover study of treatment with aspirin

Donald D. Stevenson, M.D., Warren W. Pleskow, M.D.*
Ronald A. Simon, M.D., David A. Mathison, M.D., William R. Lumry, M.D.,
Michael Schatz, M.D.,* and Robert S. Zeiger, M.D., Ph.D.*
La Jolla and San Diego, Calif.

Twenty-five ASA-sensitive patients with rhinosinusitis asthma underwent oral ASA challenges followed by desensitization to the adverse respiratory effects of ASA. We then compared the efficacy of continuous ASA treatment for their respiratory tract disease to that of a placebo treatment during a double-blind crossover study. For this group of 25 patients, there was significant improvement in nasal symptoms and a reduction in use of nasal beclomethasone during the months when they received ASA treatment. Lower respiratory tract symptoms, values of FEV₁, and the use of antiasthmatic medications including prednisone were not significantly changed during ASA treatment. Desensitization to ASA followed by ASA treatment appears to significantly alleviate symptoms of rhinosinusitis. However, only half the patients experienced improvement in their asthma symptoms during ASA treatment. (J ALLERGY CLIN IMMUNOL 73:500-507, 1984.)

25 ASA-sensitive patients with rhinosinusitis asthma underwent oral ASA challenge and desensitization

Daily ASA vs placebo (double-blind crossover study)

- Significant improvement in nasal symptoms and reduction in nasal beclomethasone with ASA treatment.
- But only 50% experienced improvement in asthma symptoms during ASA treatment.

Brief history lesson, 2001

Guest editorial

Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes

Introduction of the term

‘aspirin-exacerbated respiratory disease’

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Division of Allergy, Asthma, and
Immunology
Scripps Clinic and The Scripps
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La Jolla, CA, USA

MARIO SANCHEZ-BORGES, MD
Department of Allergology and
Clinical Immunology
Centro Medico-Docente La Trinidad
and Clinica El Avila
Caracas, Venezuela

ANDREW SZCZEKLIK, MD, PhD
Department of Medicine
Jagellonian University School of
Medicine
Krakow, Poland

Brief history lesson, 2007

Rhinitis, sinusitis, and ocular diseases

Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease

Jennifer Y. Lee, MD,^a Ronald A. Simon, MD,^b and Donald D. Stevenson, MD^c
La Jolla, Calif

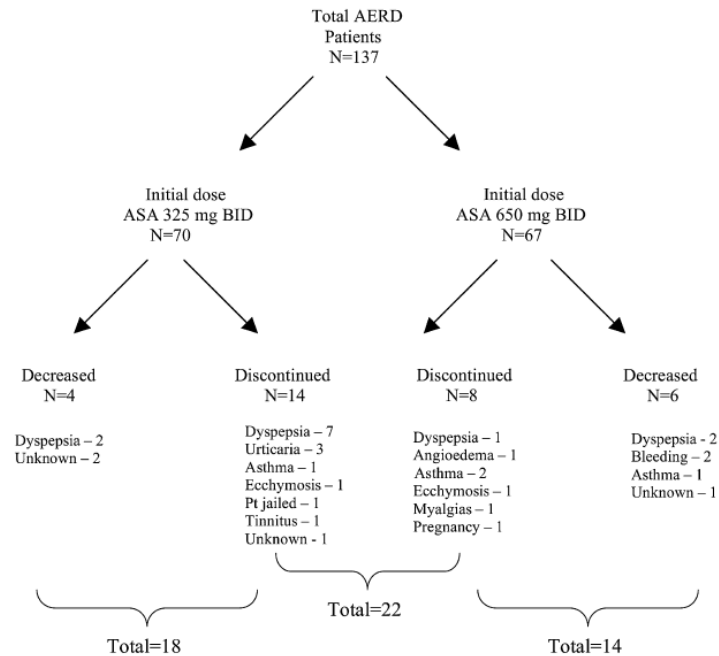


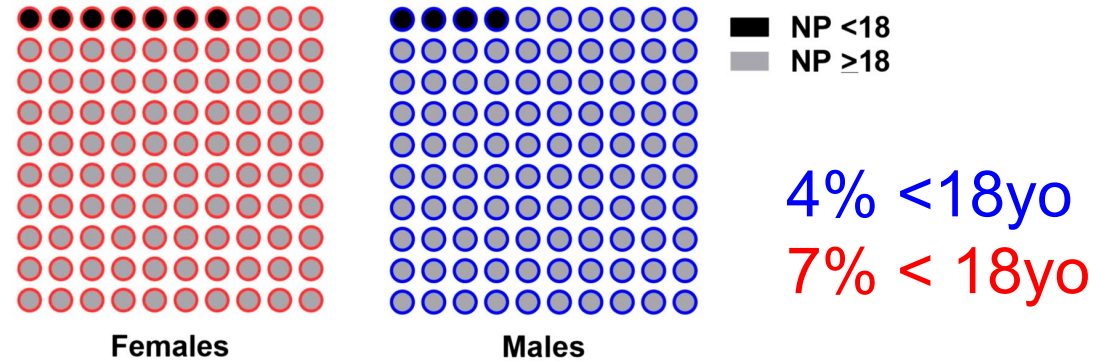
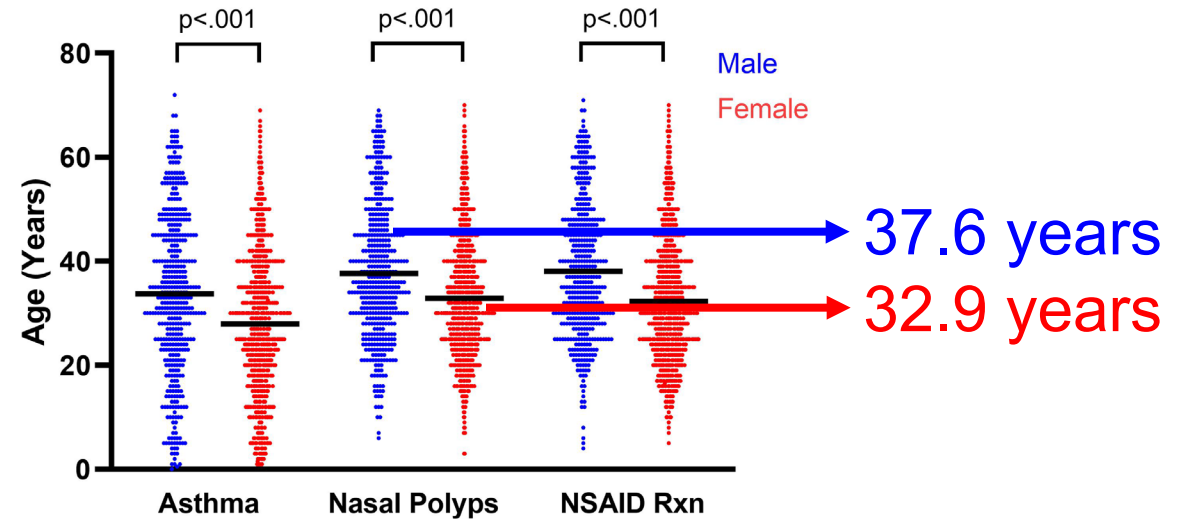
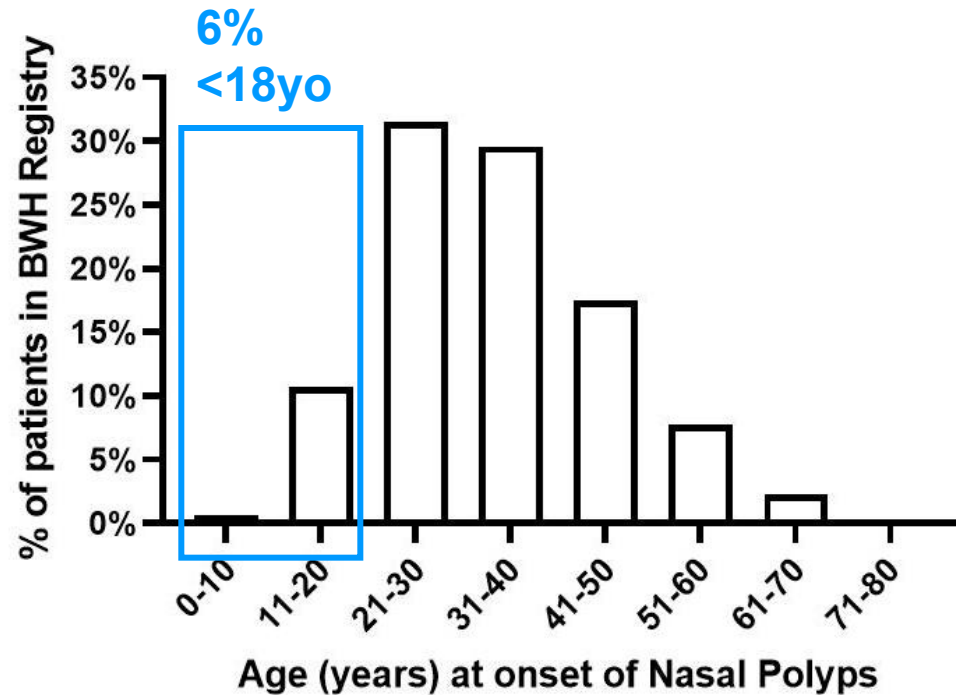
FIG 2. Pattern of discontinuation of aspirin (ASA). BID, Twice daily.

- Randomized to 650mg BID or 325mg BID → After 1 month, patients ↑d or ↓d their aspirin dose based on symptom control and continued that dose for 1 year.
- Both groups: improved anosmia, nasal & asthma symptoms; systemic corticosteroids ↓d by 3-4-fold
- 44% of 650mg BID group and 56% of 325mg BID group had AEs or discontinued aspirin. Most common AE was dyspepsia.
- **“Both dosages were efficacious, and side effects occurred in both groups at similar frequencies. Some patients initially taking 325mg BID required an increase to 650mg BID for optimal symptom control”**

Clinical implications: We recommend that patients begin daily aspirin therapy with 650mg BID and subsequently decrease to the lowest effective dosage (usually 325mg BID)

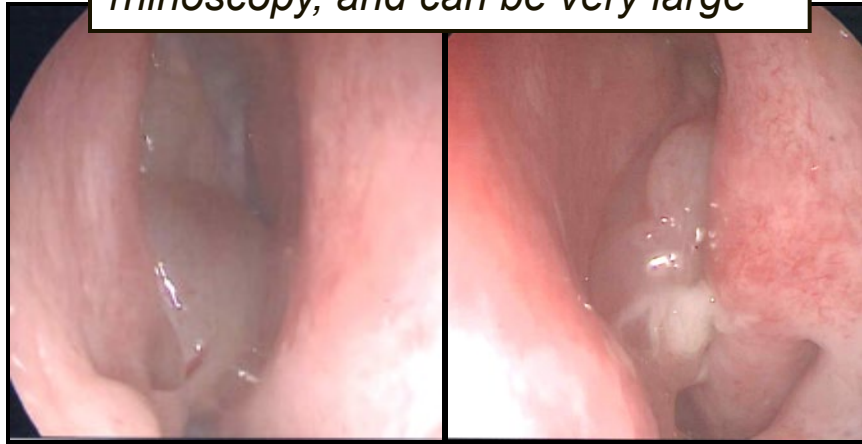
Age and gender: >2000 patients at BWH AERD Center

Largely adult-onset disease...

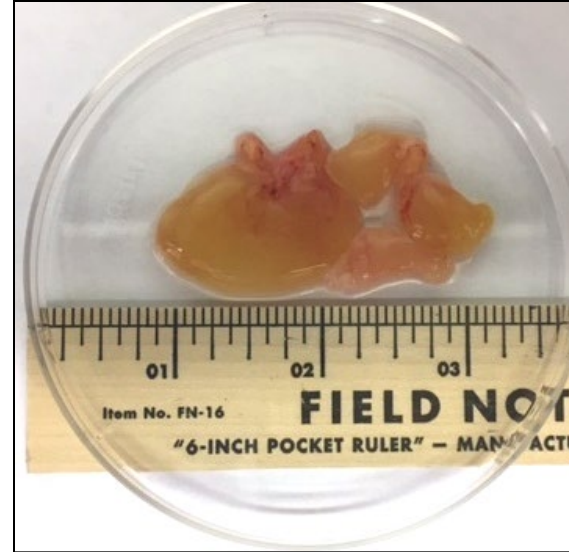


Surgery is a key treatment modality for AERD

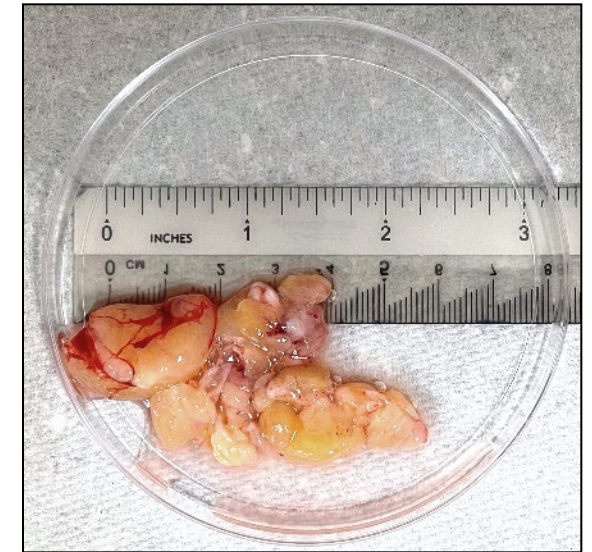
Typical appearance of polyps on rhinoscopy, and can be very large



Nasal polyps on rhinoscopy. 2015. – Selig, YK.



Nasal polyps excised.
2016 – Bhattacharyya, N.



Nasal polyps excised.
2022 – Lee, S.

Surgical histories from patients at the BWH AERD Center

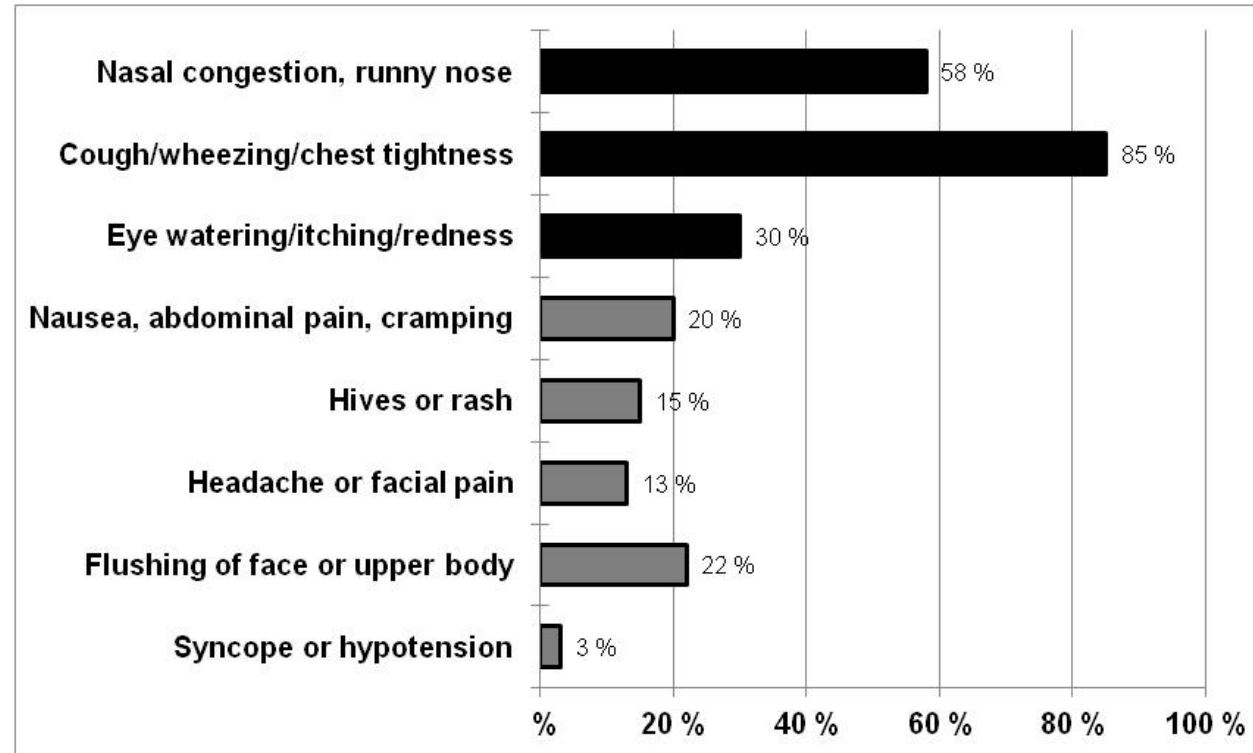
History of polyp surgery:

- 60% have had ≥ 2 surgeries
- 10% have had ≥ 5 surgeries

Rate of polyp regrowth post-op:

- 50% report regrowth ≤ 6 months
- Only 15% report no regrowth > 2 years

Reactions to NSAIDs involve more extra-pulmonary symptoms than previously thought



Any COX-1 inhibitor can cause reaction:

- aspirin, ibuprofen, naproxen, ketorolac are most common in U.S.



Aspirin challenge (to diagnose) or desensitization and high-dose oral aspirin (to treat) – BWH PROTOCOL

Time to onset of reaction from administration of provocative aspirin dose?

- “The average time to reaction following dose administration was **61 ± 22 minutes**”
- “Mean time in minutes to the onset of the hypersensitivity reaction after provoking dose = **43 ± 5.7 minutes**”

[J Allergy Clin Immunol Pract.](#) 2019 Apr;7(4):1174-1180. doi: 10.1016/j.jaip.2018.10.032. Epub 2018 Nov 2.

A 1-Day, 90-Minute Aspirin Challenge and Desensitization Protocol in Aspirin-Exacerbated Respiratory Disease

Geneva A DeGregorio ¹, Joseph Singer ², Katherine N Cahill ³, Tanya Laidlaw ⁴

Affiliations + expand

PMID: 30391549 PMID: PMC6456426 DOI: 10.1016/j.jaip.2018.10.032

[Observational Study](#) [J Allergy Clin Immunol Pract.](#) 2019 May-Jun;7(5):1580-1588. doi: 10.1016/j.jaip.2018.12.014. Epub 2018 Dec 21.

Sinus Surgery Is Associated with a Decrease in Aspirin-Induced Reaction Severity in Patients with Aspirin Exacerbated Respiratory Disease

Elina Jerschow ¹, Matthew L Edin ², Yuling Chi ³, Beth Hurst ⁴, Waleed M Abuzeid ⁵, Nadeem A Akbar ⁵, Marc Gibber ⁵, Marvin P Fried ⁵, Weiguo Han ³, Teresa Pelletier ³, Zhen Ren ⁶, Taha Keskin ⁵, Gigia Roizen ⁵, Fred B Lih ², Artiom Gruzdev ², J Alyce Bradbury ², Victor Schuster ⁵, Simon Spivack ⁵, David Rosenstreich ⁵, Darryl C Zeldin ²

Affiliations + expand

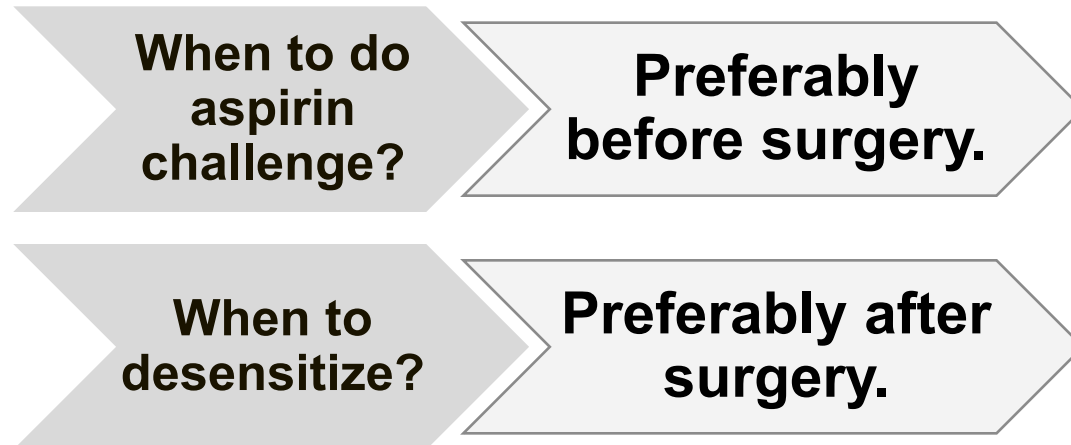
PMID: 30580047 PMID: PMC6511299 DOI: 10.1016/j.jaip.2018.12.014



Desensitization, then high-dose oral aspirin to delay polyp regrowth

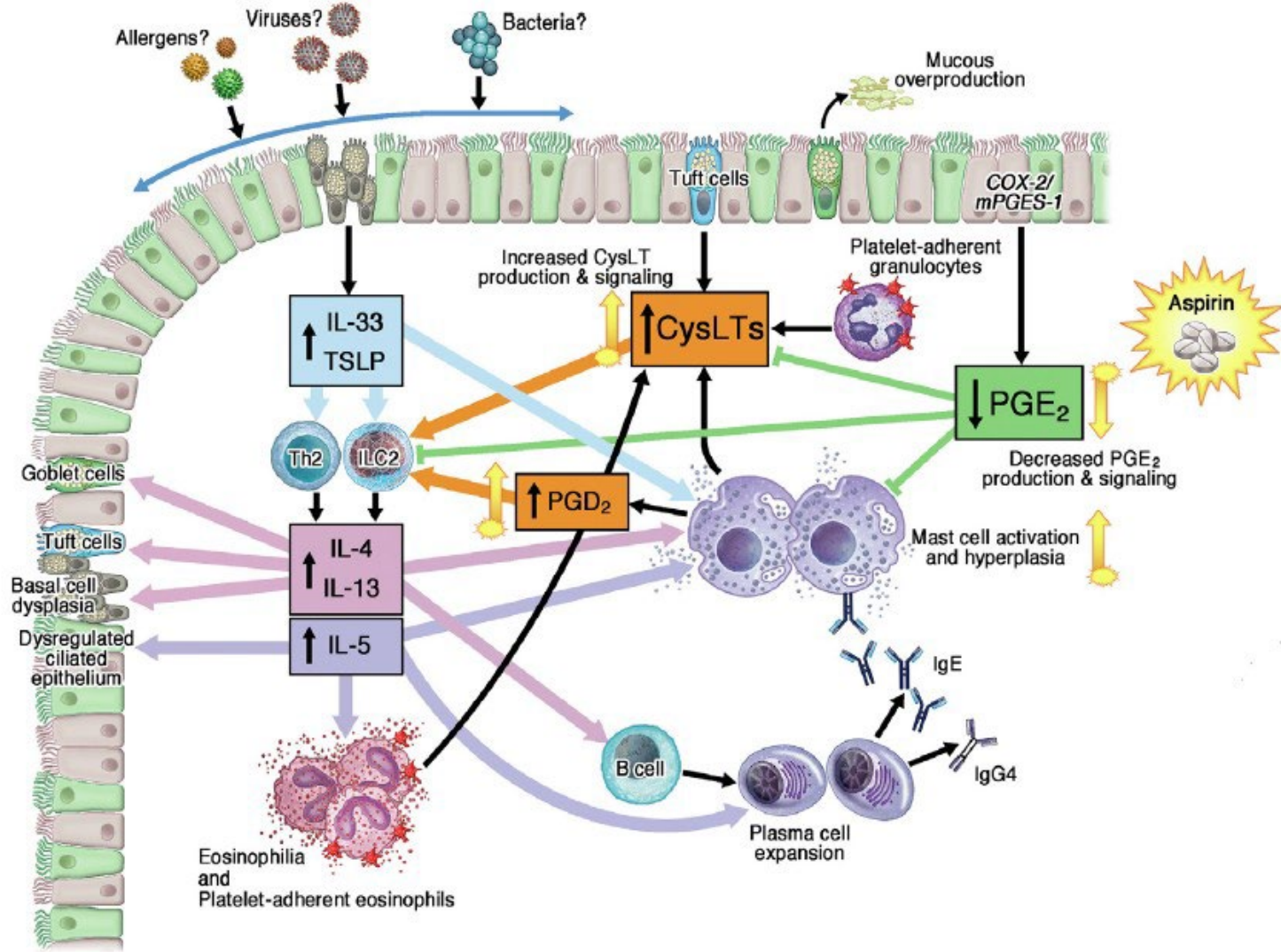
- 60ish% patients report improvement after 6 months of high-dose aspirin
- ↓nasal symptoms/congestion, some return of smell
- **Lower rates of polyp recurrence post-operatively**

Stevenson, et al. JACI 1996
Rozsasi, et al. Allergy 2008
Mizankowska-Mogilnicka, et al. JACI 2014



Huang G, et al. JACI IP 2019
Jerschow E, et al. JACI IP 2019

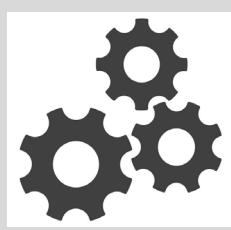
AERD is a disease of Type 2 Inflammation



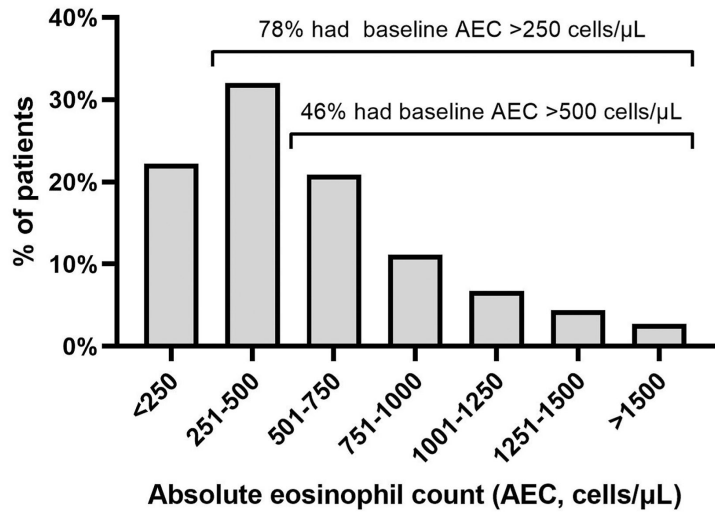
Lots of things are abnormal.

But who can we “blame” for the inflammation in AERD?

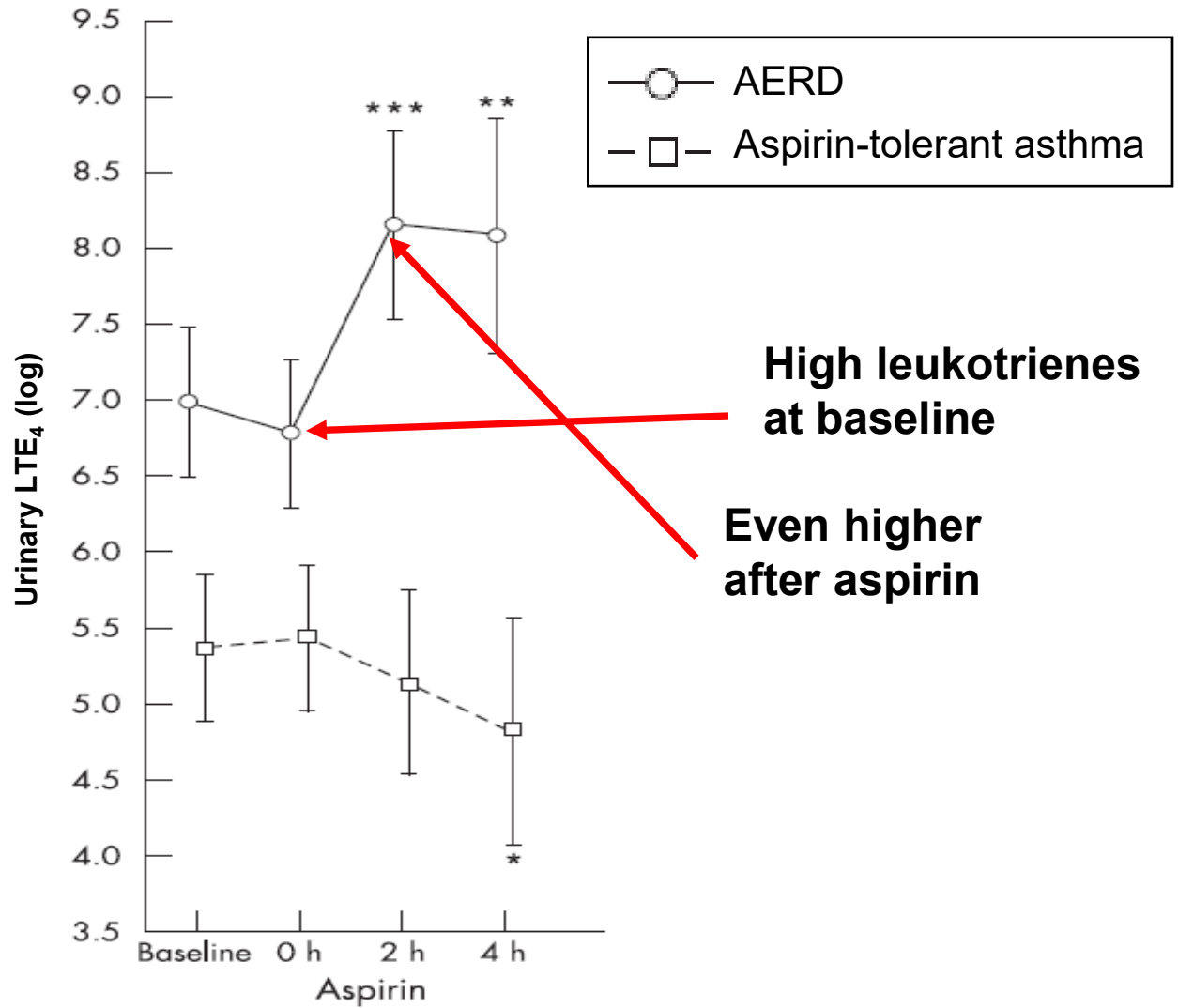
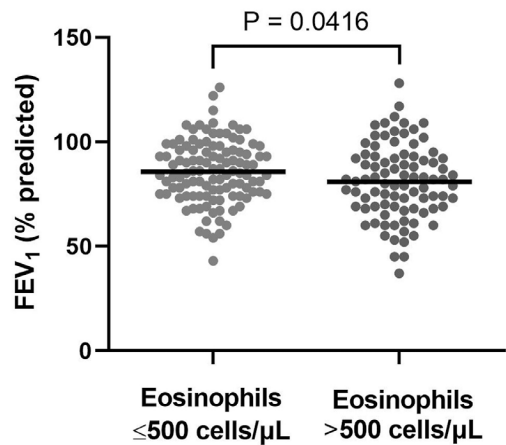
Eosinophils and leukotrienes have been at the center of conversations about AERD

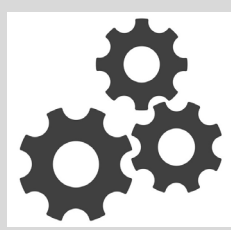


Blood eosinophilia is common



Blood eosinophils relate to FEV1





Leukotriene modifying drugs in AERD

- **Zileuton** (5-LO inhibitor) and **montelukast** (cysLT1R blockade) can improve AERD symptoms at baseline

- Dahlen B, Szczeklik A et al. AJRCCM 1998; Dahlen S, et al. AJRCCM 2002; Micheletto C. Allergy 2004

Ta and White
JACI IP, 2015
(190 patients)

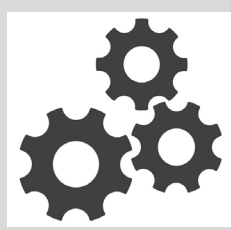
**28% found zileuton
“extremely effective”**

only 24% had ever been on zileuton

Zileuton can increase the provoking dose of aspirin or occasionally block reactions completely

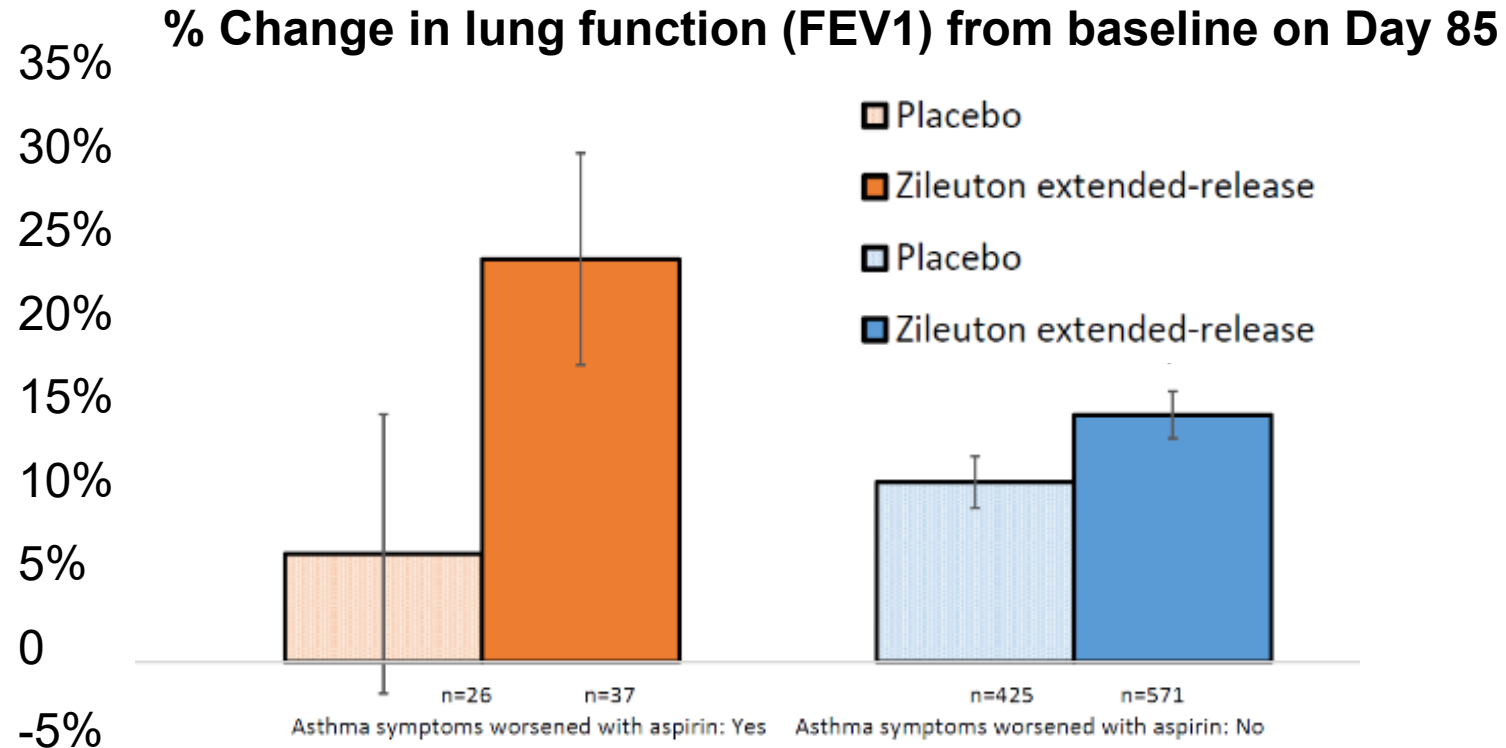
E Israel, AmRevRespirDis, 1993

➤ *Very useful for GI symptoms during aspirin reaction*



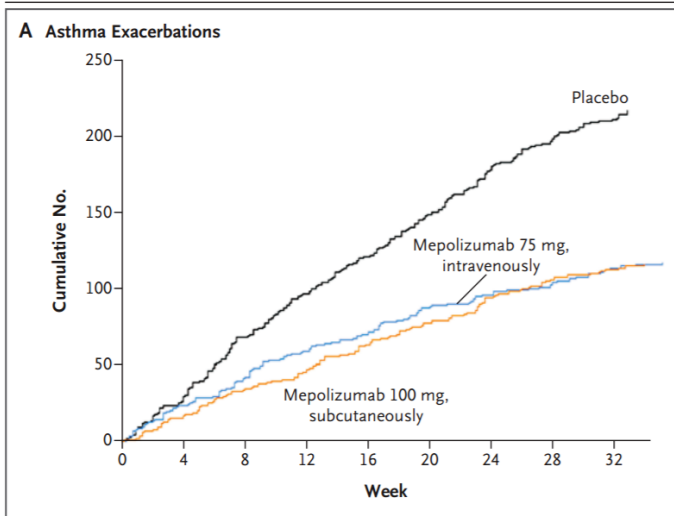
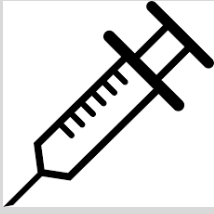
Zileuton is more effective in patients with AERD than in aspirin-tolerant asthma

“Efficacy of Zileuton in Patients with Asthma and History of Aspirin Sensitivity: A Retrospective Analysis of Data from Two Phase 3 Studies”

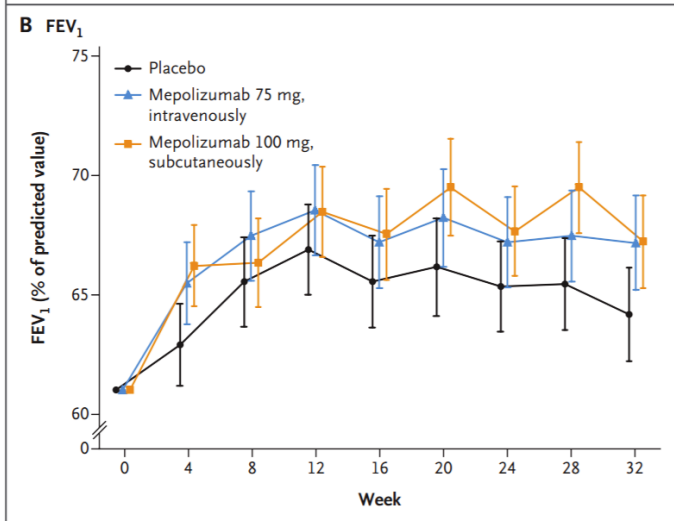


AERD patients

Mepolizumab (anti-IL-5) improves asthma control & lung function in eosinophilic asthma, reduces nasal polyp scores



- ↓ 47-53% reduction in asthma exacerbations
- >70% reduction in pts with eosinophils ≥ 500 cells/ μ L



- ↑ 98-100mL increase in FEV1
- 130-185mL increase in pts with eos ≥ 500 cells/ μ L

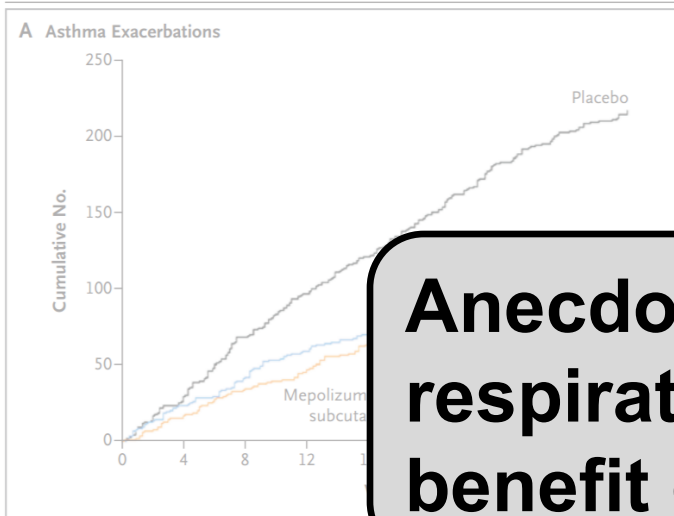
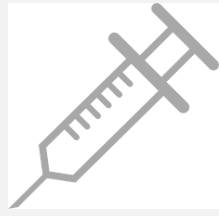
Nucala (mepolizumab) is the first anti-IL5 biologic to report positive phase 3 results in patients with nasal polyps

SYNAPSE; Phase 3 nasal polyps

- 407 patients total
 - ↓ NP score of 0.73 at 52wks
 - No significant improvement in smell (UPSIT)
- 108 AERD patients
 - ↓ NP score of 0.89 at 52wks

Han JK, et al. Lancet Resp Med 2021

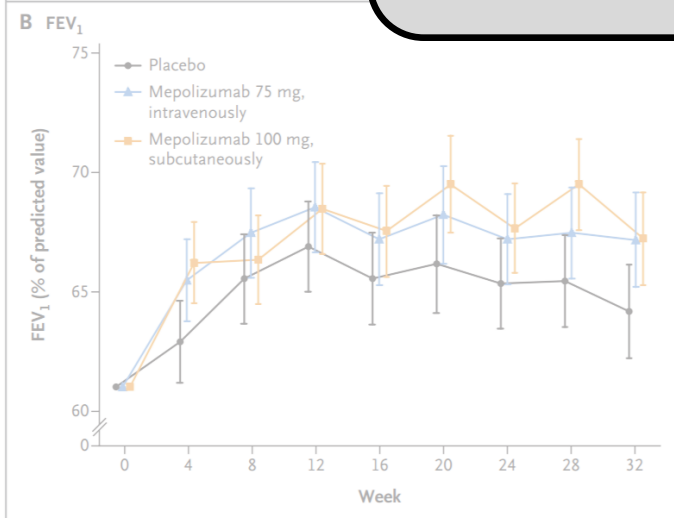
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Anecdotal disconnect between lower respiratory and upper respiratory benefit of mepolizumab in AERD



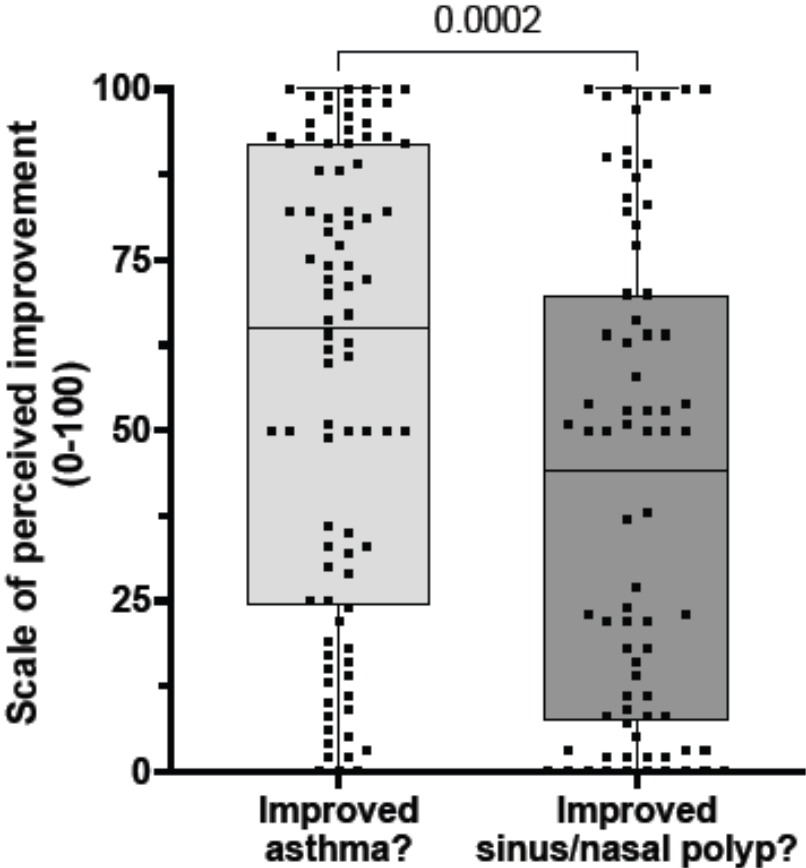
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Phase 3 nasal polyps patients total
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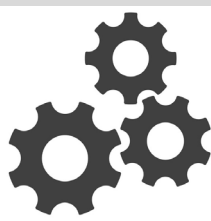
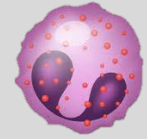
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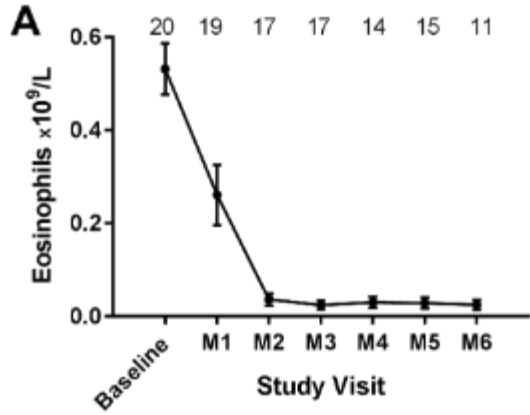
Mepolizumab improves perceived asthma control more than perceived sinus/nasal polyp control



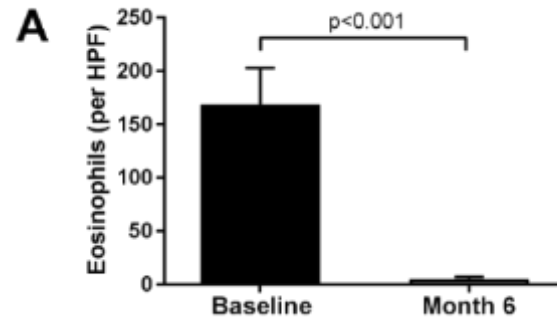
Dexpramipexole in CRSwNP – how important are eosinophils?



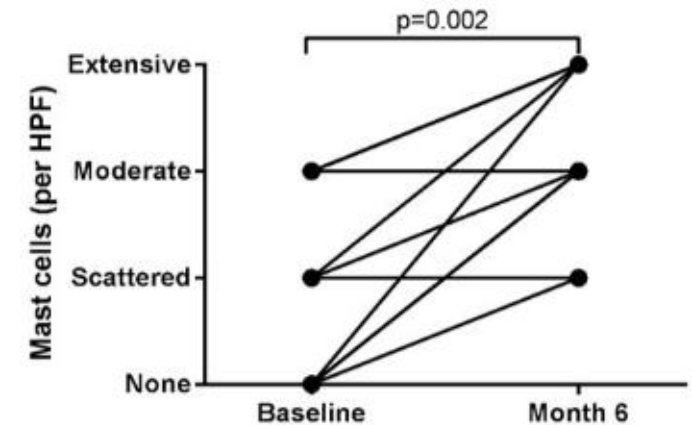
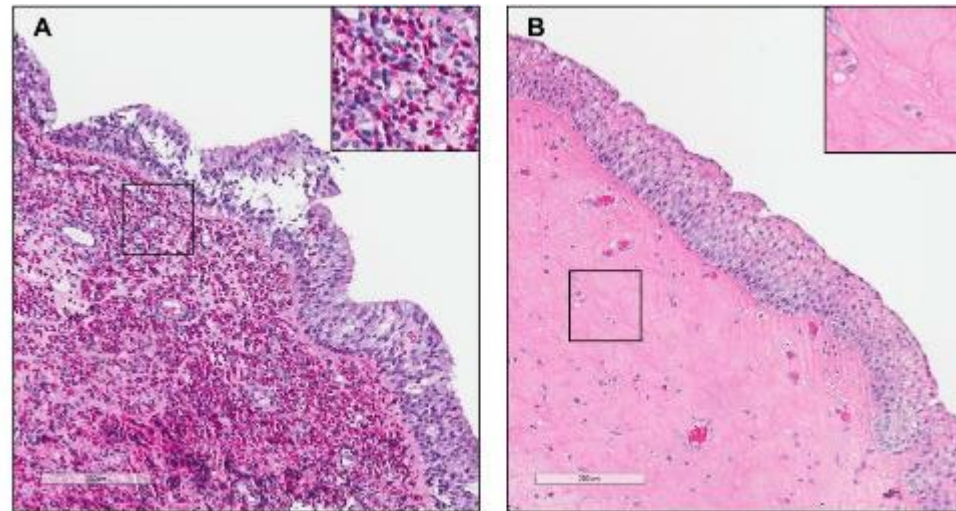
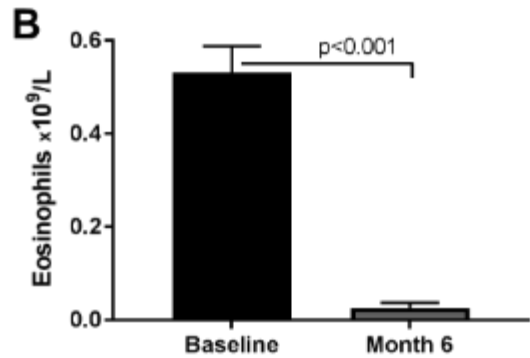
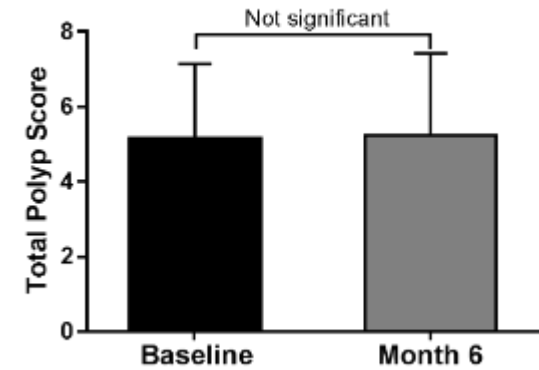
Blood eosinophils decrease



Polyp eosinophils decrease



No improvement in polyp size

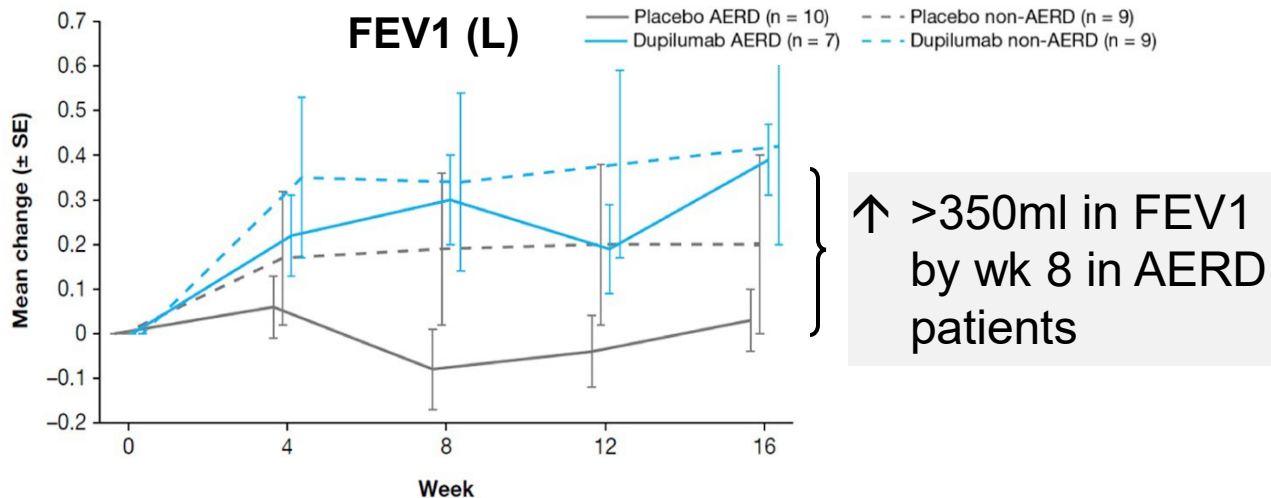
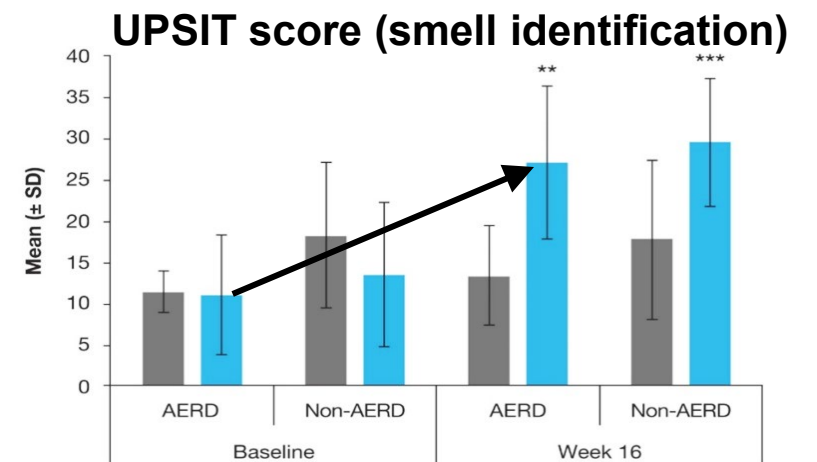
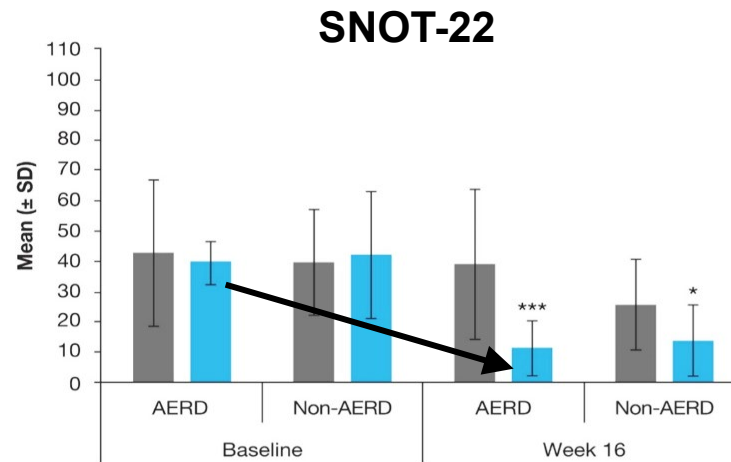
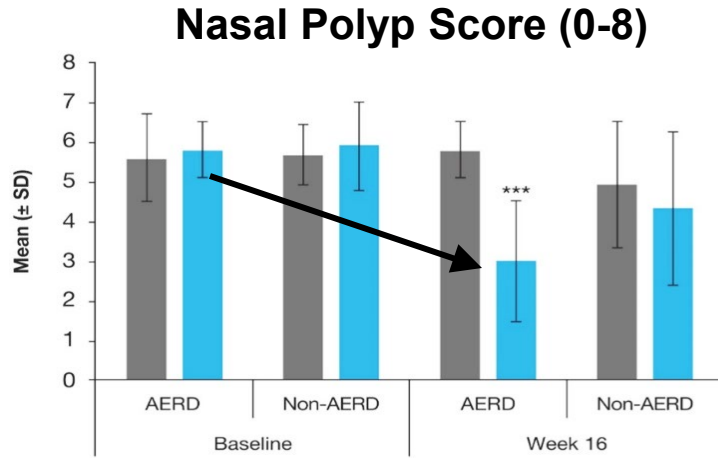


Dupilumab (anti-IL4R α) in AERD

Re-analysis of Phase 2 study;
19/60 subjects had aspirin sensitivity



■ Dupilumab ■ Placebo

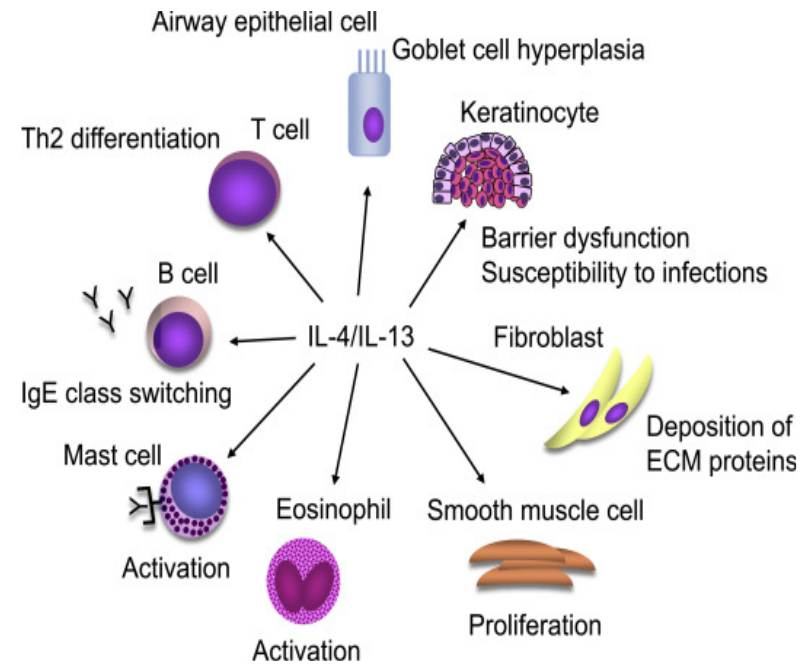
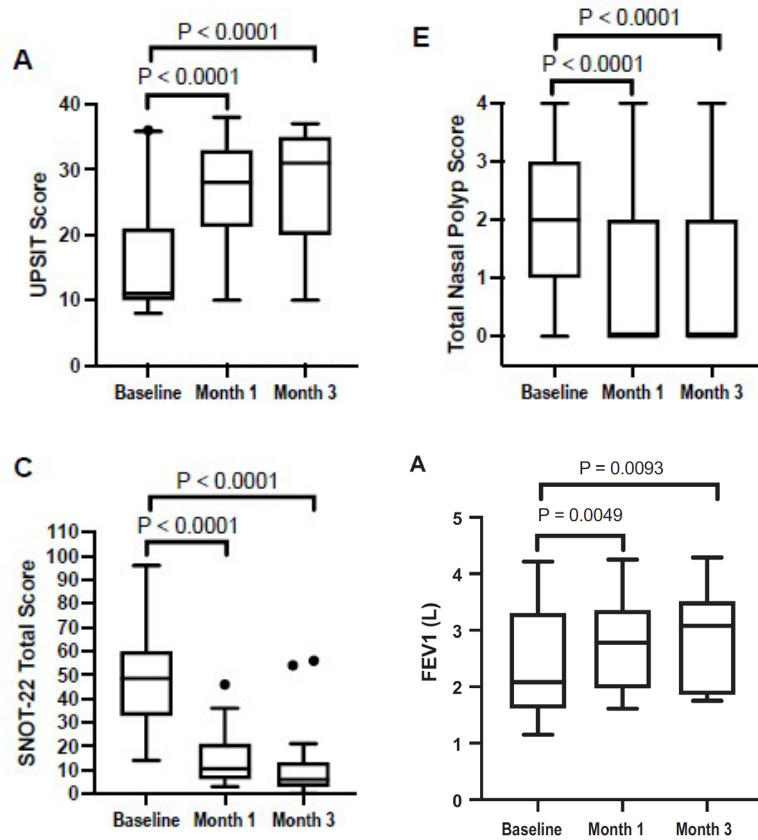


↑ >350ml in FEV1 by wk 8 in AERD patients

SINUS-52; Phase 3 nasal polyps

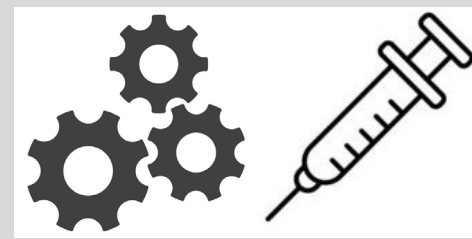
- 448 patients total
 - ↓ NP score of 2.06 at 24wks
 - Smell improvement (UPSIT) of 11 pts.
- 79 AERD patients
 - ↓ NP score of 2.54 at 24wks

Anti-IL4R α (dupilumab) rapidly improves clinical upper & lower respiratory outcomes

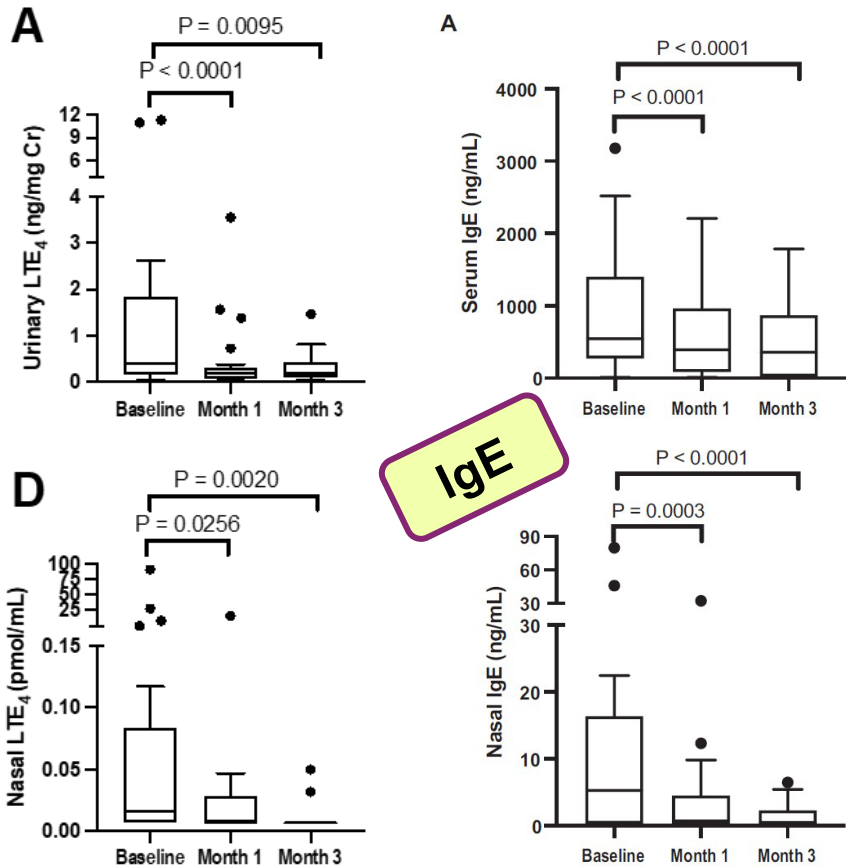


Matsunaga K et al. Allergy Int 2020

Mechanism of dupilumab-induced improvement in AERD? – pilot trial

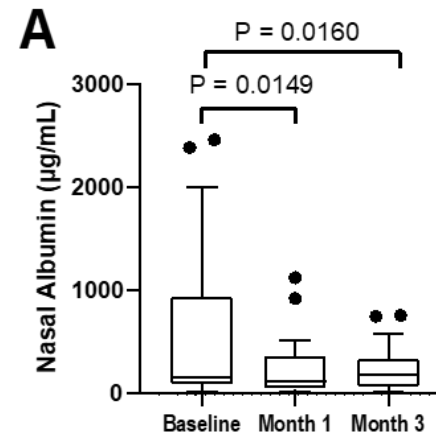


Mast cell improvement



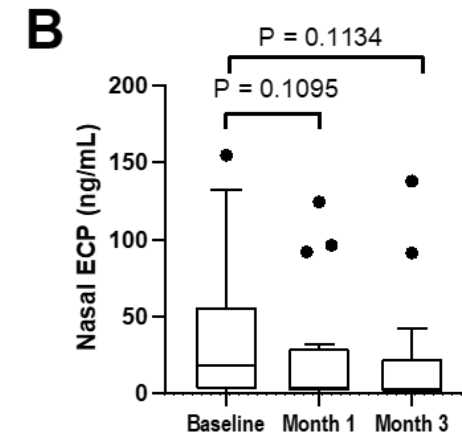
Epithelial barrier improvement

↓ Nasal albumin



Eosinophil

NO Δ in Nasal ECP



Diet to reduce omega-6 fatty acids (and increase omega-3) can decrease leukotrienes and improve symptoms in AERD

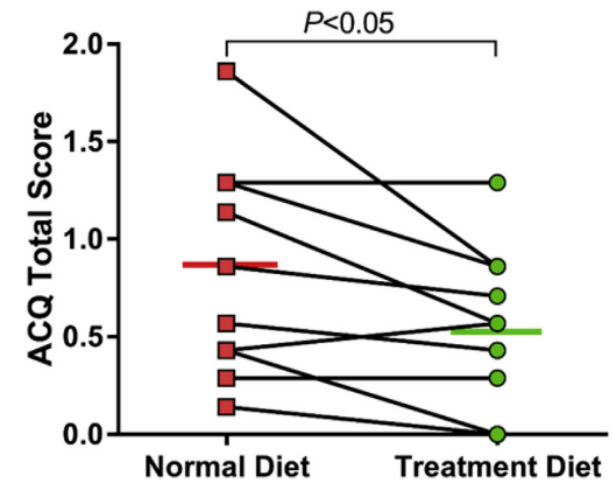
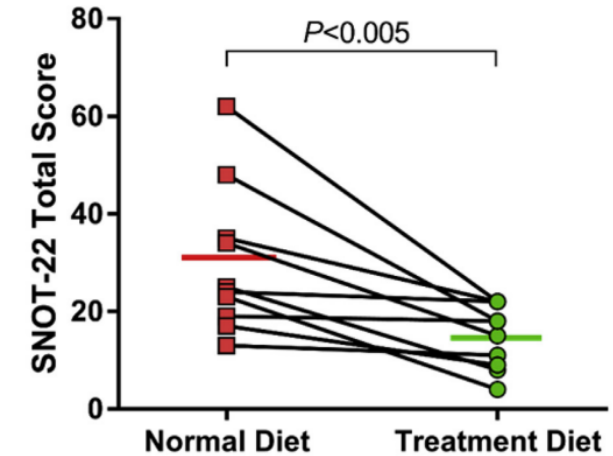


Good:

- Wild-caught cold-water fish (salmon, herring, tuna)
- Fat-free dairy, egg white
- Leafy green vegetables
- Most vegetables and fruits
- Many beans, some grains

Bad:

- Vegetable oils (corn, soybean, safflower)
- Margarine
- Meats if animals ate corn/soy
- Eggs/dairy if animals ate corn/soy



Diet to reduce omega-6 fatty acids (and increase omega-3) can decrease leukotrienes and improve symptoms in AERD



Good:

Wild-caught cold-water fish

(s)

Fat-free

Leafy green

Most veg

Many be

I don't like the "low-salicylate" diet. It shouldn't work. Why not?

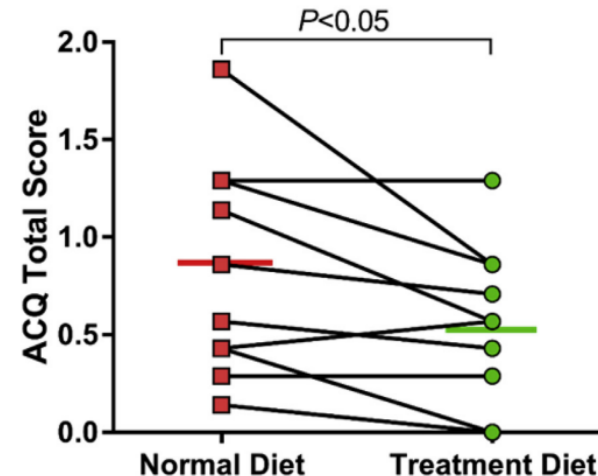
Bad:

Vegetable oils (corn, soybean, safflower)

Margarine

Meats if animals ate corn/soy

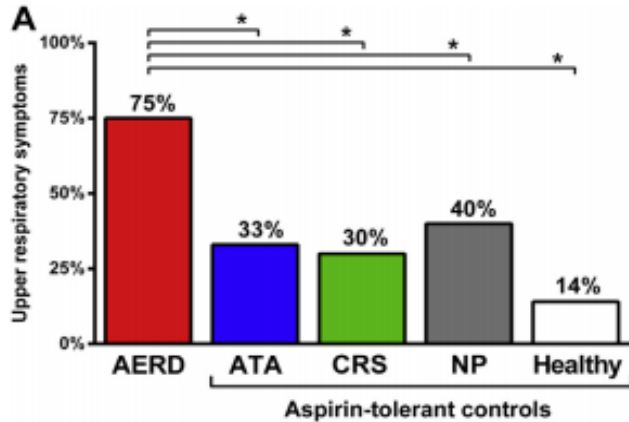
Eggs/dairy if animals ate corn/soy



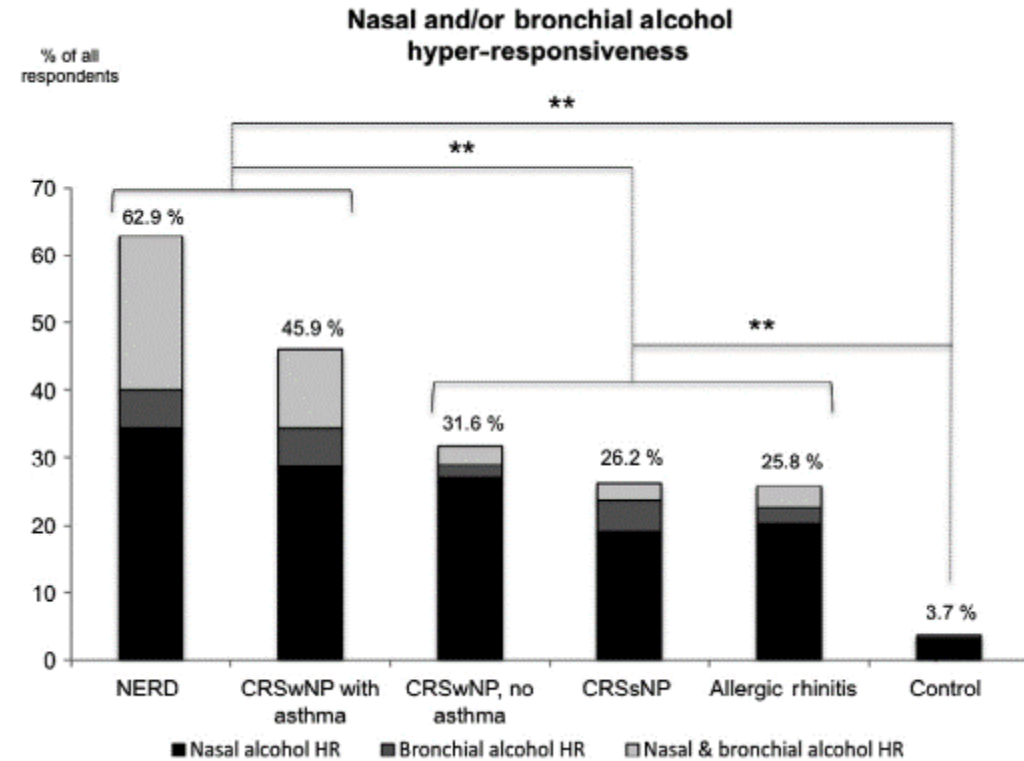
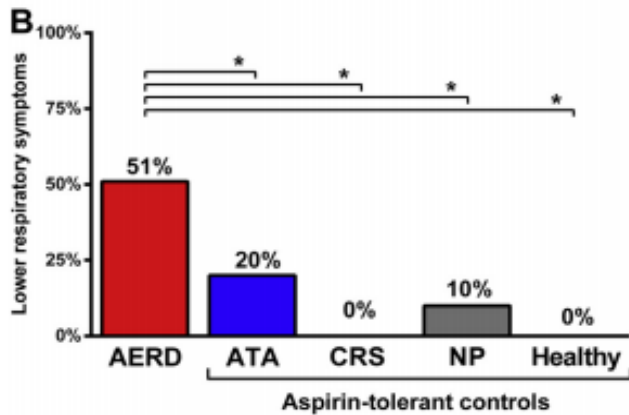


Clinical clue: Respiratory reactions to alcohol

Upper respiratory reactions



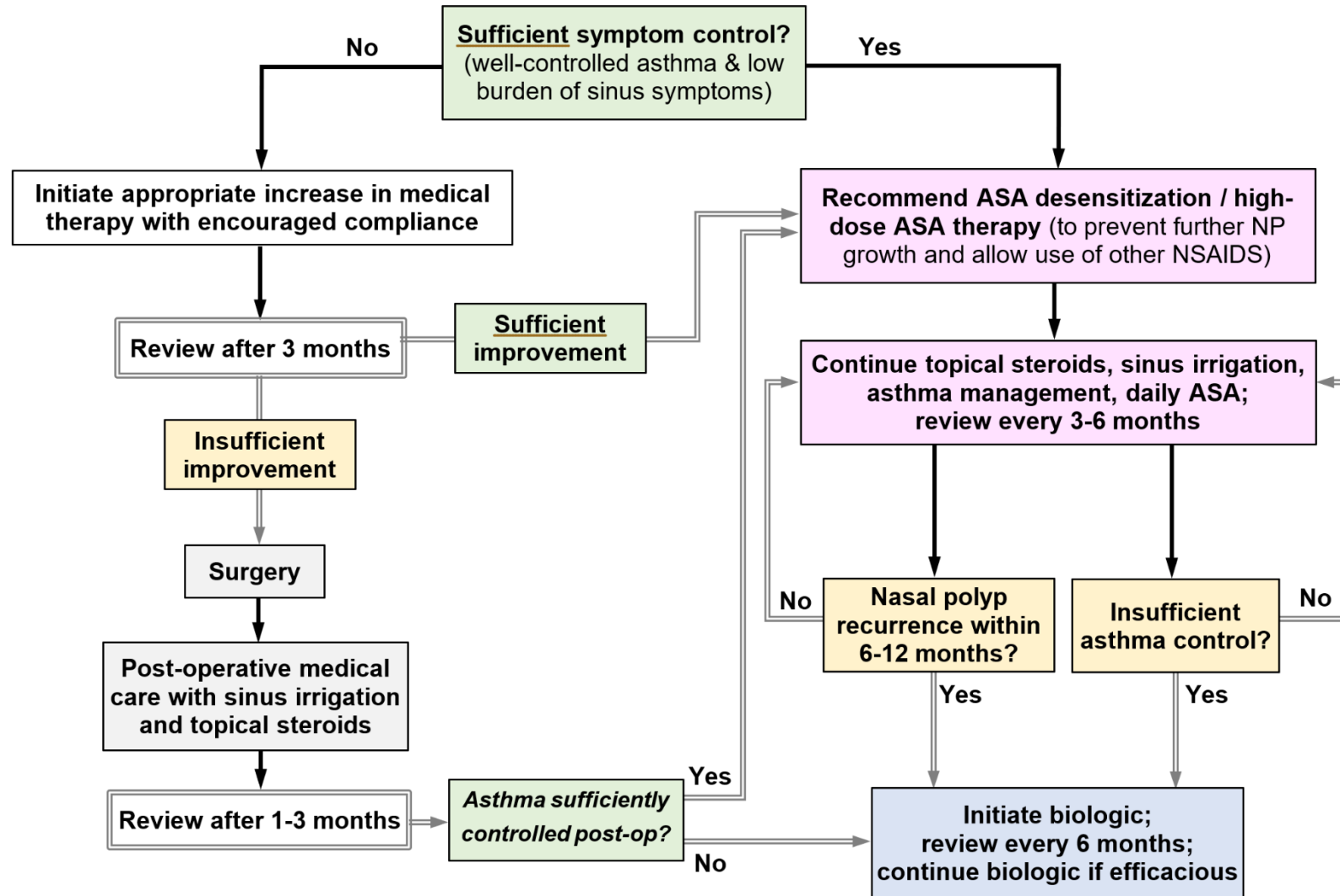
Lower respiratory reactions



De Schryver E. Clin&ExperAll 2016

- Wine, beer, and liquor could all trigger reactions
- For some, a “few sips” was sufficient
- Symptoms within 1 hour of alcohol consumption

Treatment algorithm for AERD today



Adapted from Bachert, Desrosiers, Hellings, Laidlaw, JACI IP 2021

Clinical

Diagnosis

- Ask adult asthmatic patients about nasal polyps, sense of smell, COX-1 inhibitor tolerance, alcohol intolerance

Aspirin

- Recognize classic reactions to COX-1 inhibitors, and role for aspirin challenge and aspirin desensitization

Treatments

- Therapeutic role for leukotriene modification and respiratory biologics in AERD

Mechanism

Cells

- **Mast cell & epithelial cell** dysregulation → key immune mechanisms that drive AERD
- Role of **eosinophils** less clear

Mediators

- **CysLTs** contribute to low FEV₁ & aspirin reactions
- **IL-4/IL-13** drive substantial pathology
- Role of **IL-5 & IL-6** less clear



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