Aspirin-Exacerbated Respiratory Disease

Diagnosis and Treatment

Tanya M. Laidlaw, MD

Division of Allergy and Clinical Immunology, Brigham and Women's Hospital
Director of Translational Research in Allergy, Director of BWH AERD Center
Associate Professor of Medicine, Harvard Medical School

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Laidlaw Lab
RESPIRATORY INFLAMMATION
investigate . discover . treat

HARVARD MEDICAL SCHOOL

Conflict of Interest Disclosure

- Relevant financial relationships with commercial interests in the preceding 12 months:
  Sanofi, Regeneron, GSK, AstraZeneca


AERD

Overview of slides

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Clinical disease, with a case, and findings from our cohort at BWH AERD Center

Reactions to NSAIDs and aspirin challenge/desensitization

Mechanism and role of leukotrienes

Newest treatment options – biologics and diet

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

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Asthma

Nasal Polyps

Reactions to aspirin & COX-1 inhibitors

- Eosinophils in tissues and blood
- Sinus disease is severe -- (Anosmia, polyp recurrence)

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

Classic AERD = 35 year-old “Danielle”

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- Childhood → healthy, no asthma or allergies
- 23yo → “really bad cold” and persistent nasal congestion
- 24yo → asthma, continued congestion, lost sense of smell and taste
- 25yo → saw ENT surgeon, was “full of polyps”, had 1st polyp surgery (great improvement!), but polyps returned in 6 months
- 25yo → **Cold-flu tablet** – 2 h later sneezed, chest tightness, wheezing
  → 3 mo later **ibuprofen** – to ER for albuterol and IV steroids
  → 6 months later took **Aleve** – same reaction

- Polyp surgeries: 25yo, 27yo, (no surgery while had 2 kids), 33yo, 35yo

- Now → Inhaled steroids, montelukast, steroid sprays, loratidine, Albuterol 3-4 days/wk, no sense of smell, antibiotics for sinusitis 2-3 times a year, polyps are back

Age and gender: >2000 patients at BWH AERD Center

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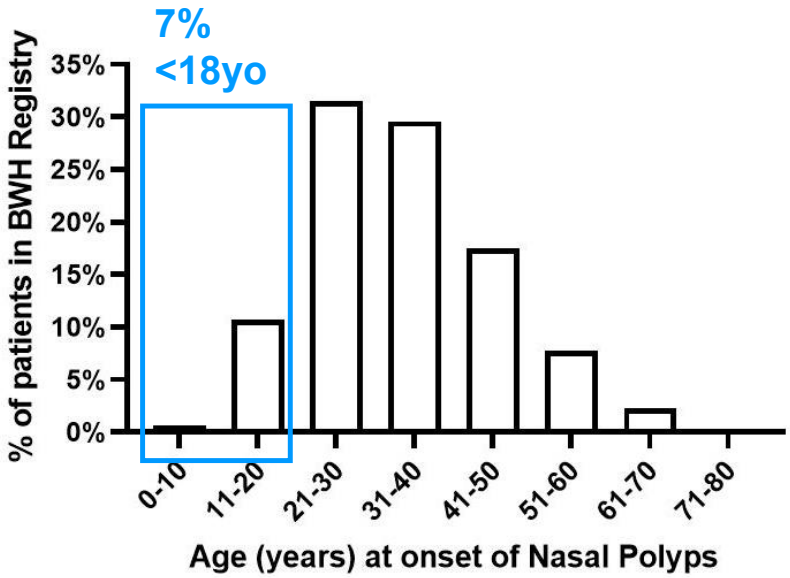
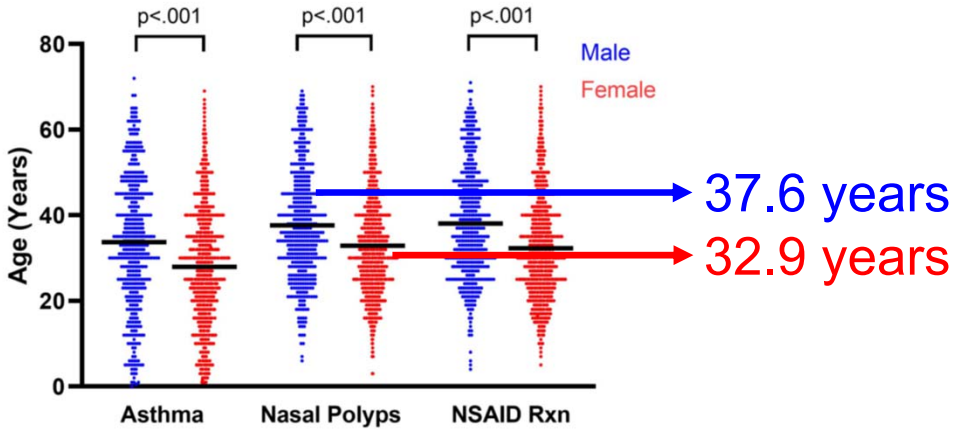
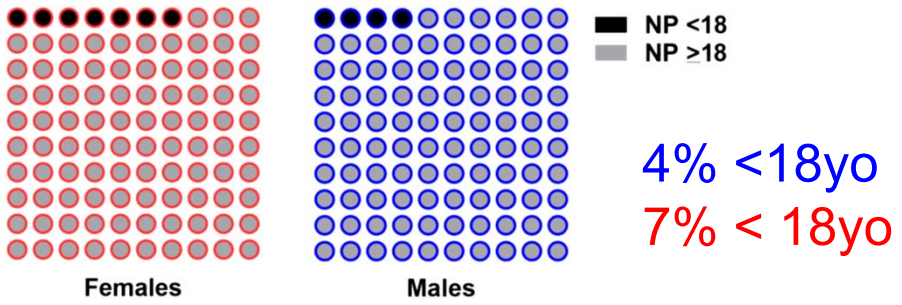
Largely adult-onset disease…







Bensko JC, et al. JACI IP, 2022

Surgery is a key treatment modality for AERD

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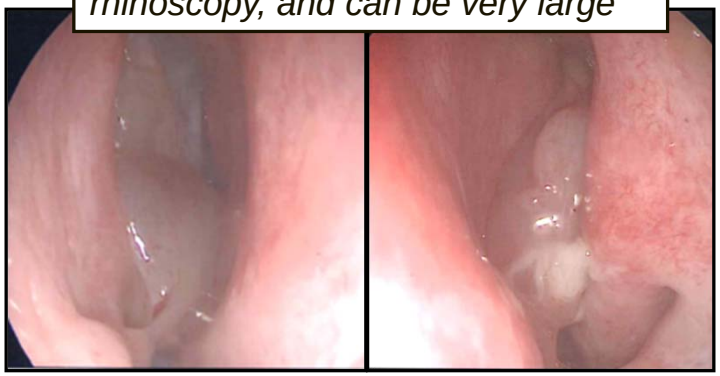
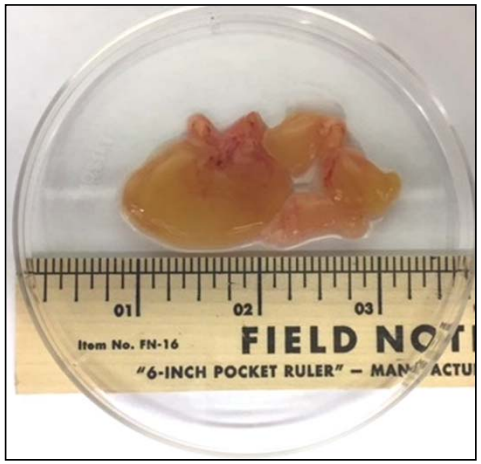
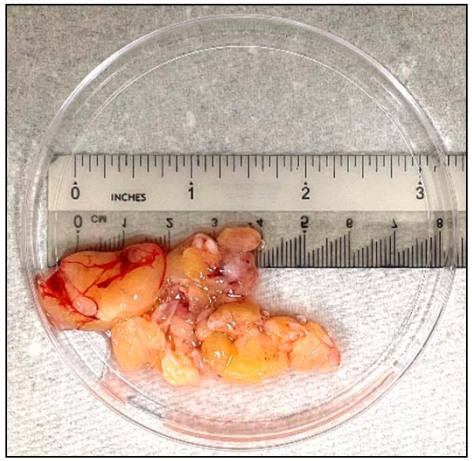
Typical appearance of polyps on rhinoscopy, and can be very large



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

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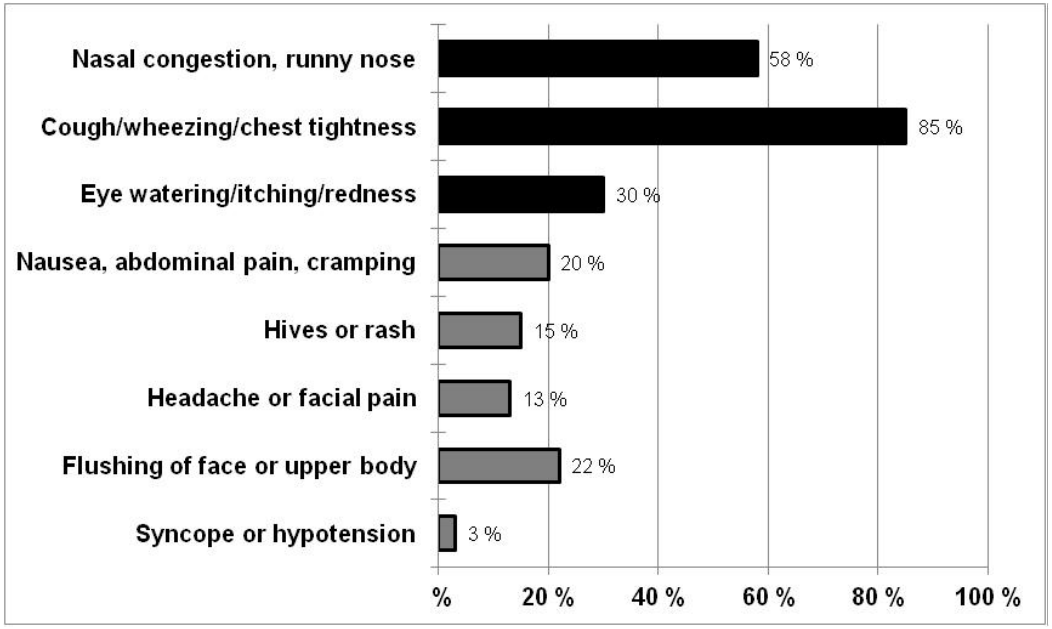


Any COX-1 inhibitor can cause reaction:

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

Reactions to acetaminophen/Tylenol?

- 3-6% of AERD patients have some reaction to 650mg
  Szczeklik A, et al. JACI 1977;60:276-84
- 34% of AERD patients react (generally mild) to >1000mg
  Settipane RA, et al. JACI 1995;96:480-5

Reactions to celecoxib?

Celecoxib is contraindicated: "In patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs."

TABLE I. Reactivity to selective COX-2 inhibitors with single-blind or double-blind placebo-controlled oral challenges in patients with NSAID-induced respiratory reactions

	No. of reactions	No. of DPT	Percentage of reactions
Celecoxib (n = 14)	0	297	0
Rofecoxib (n = 15)	1*	356	0.28
Etoricoxib (n = 2)	0	88	0
Parecoxib (n = 2)	0	12	0
Valdecoxib (n = 0)	N/A	N/A	N/A
COX-2 inhibitors combined	1	753	0.13

DPT, Drug provocation test; *n*, number of studies; *NSAID*, nonsteroidal anti-inflammatory drug.
*Transient urticaria with 5 mg, but tolerated higher doses without symptoms.

Li L, et al. JACI-IP 2019

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

- **Daily aspirin to maintain desensitization –**
  ★ benefits occur only if aspirin is taken regularly ★

Challenge

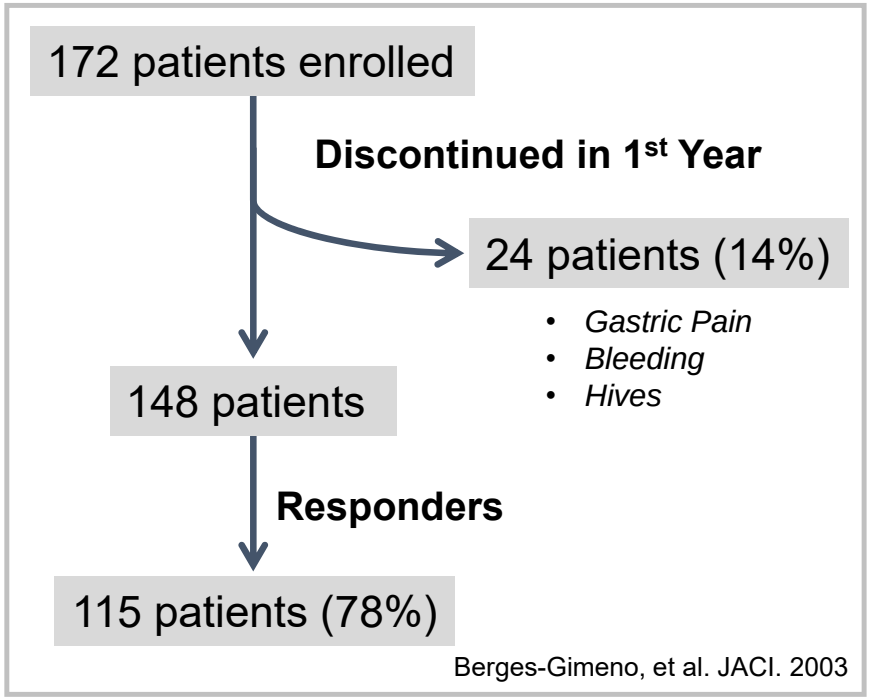
Provocation of symptoms

Desensitization

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

- 67% patients report improvement after 6 months of high-dose aspirin
- Lower rates of polyp recurrence post-operatively
- ↓SNOT-20, ↑PNIF, some return of smell

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



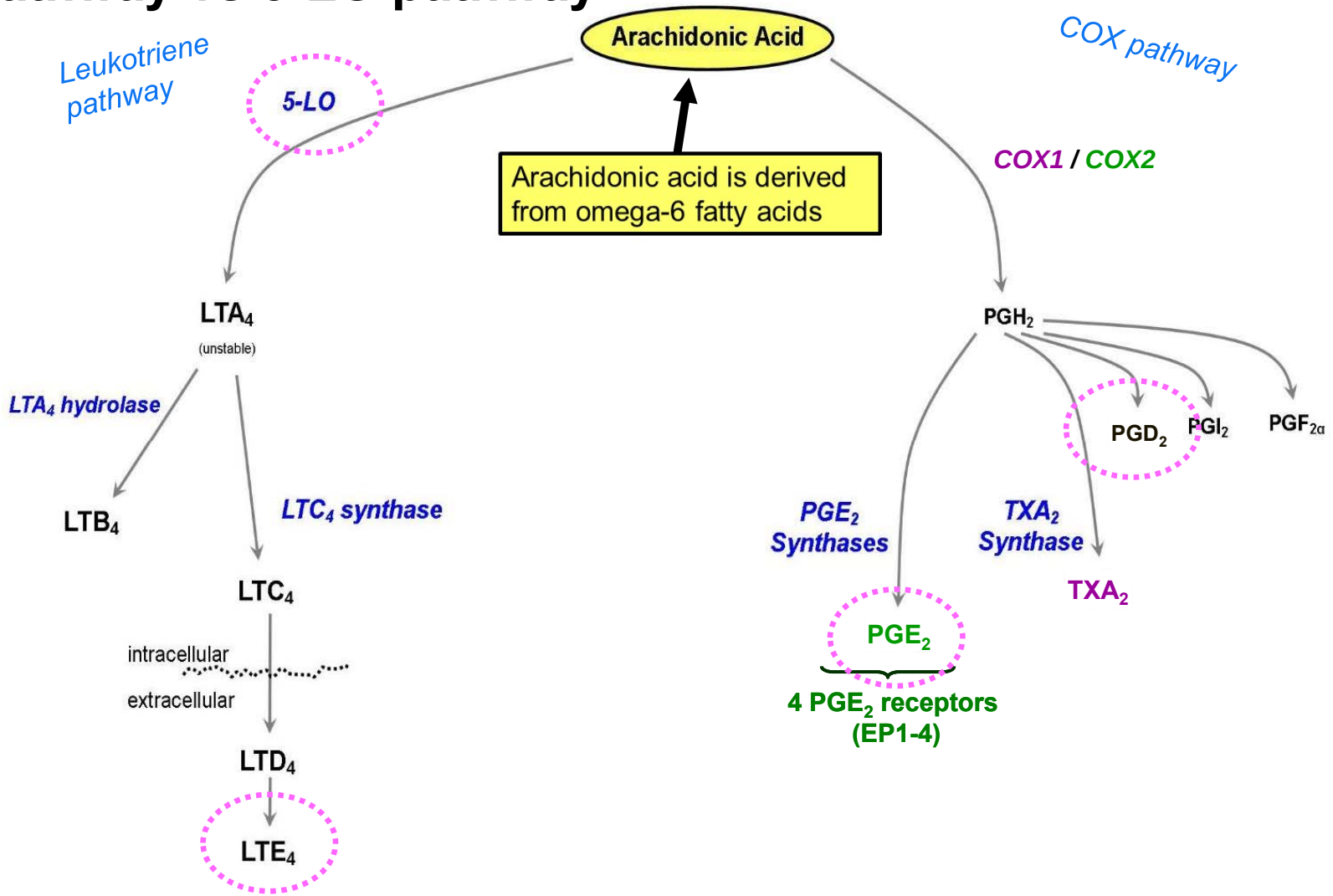
When to do aspirin challenge?

- **Preferably before surgery.**

When to desensitize?

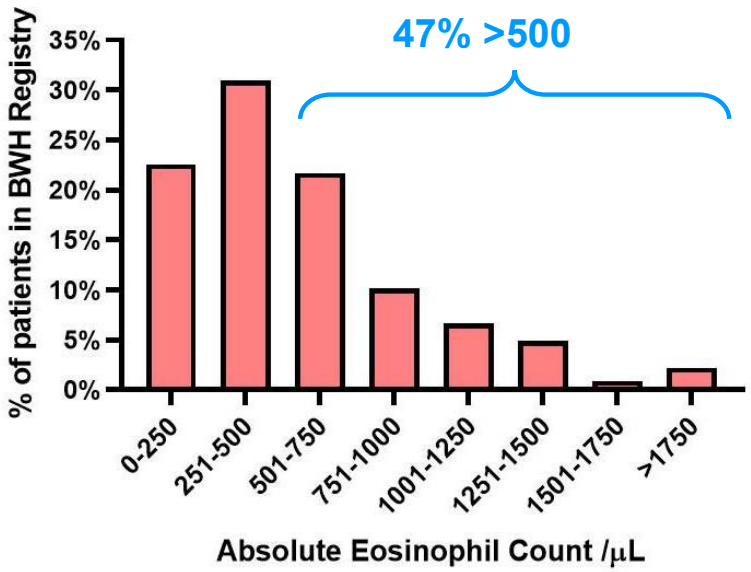
- **Preferably after surgery.**

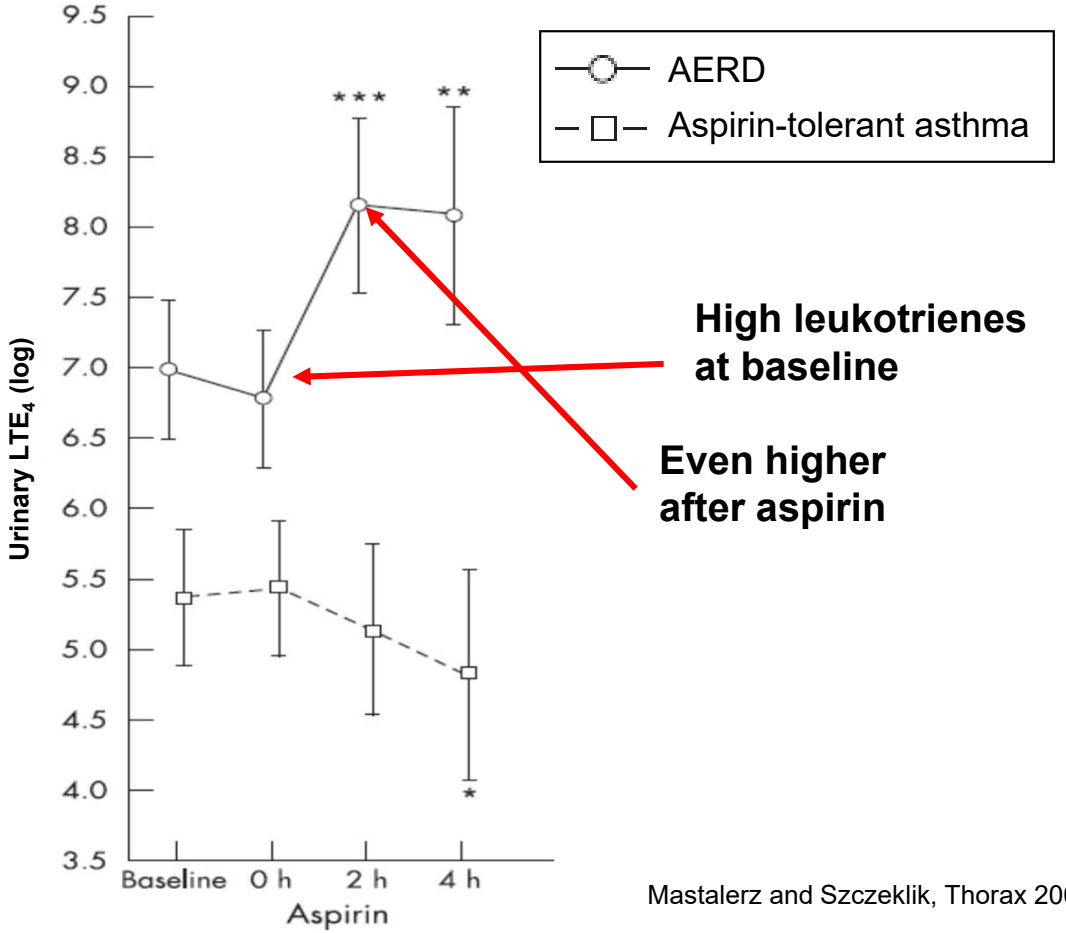
COX pathway vs 5-LO pathway



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

Blood eosinophilia is common





Mastalerz and Szczeklik, Thorax 2008

Leukotriene modifying drugs in AERD

- **Zileuton** (5-LO inhibitor) and **montelukast** (cysLT1R blockade) improve AERD symptoms at baseline
  - **Zileuton** improves FEV1, decreases albuterol need, improves smell
  - **Montelukast** improves FEV1, nasal symptom scores
    - Dahlen B, Szczeklik A et al. AJRCCM 1998
    - Dahlen S, et al. AJRCCM 2002
    - Micheletto C. Allergy 2004

- 28% found zileuton “extremely effective” (only 24% had ever been on zileuton)
- 15% found montelukast “extremely effective” (almost 90% had been on one of these)

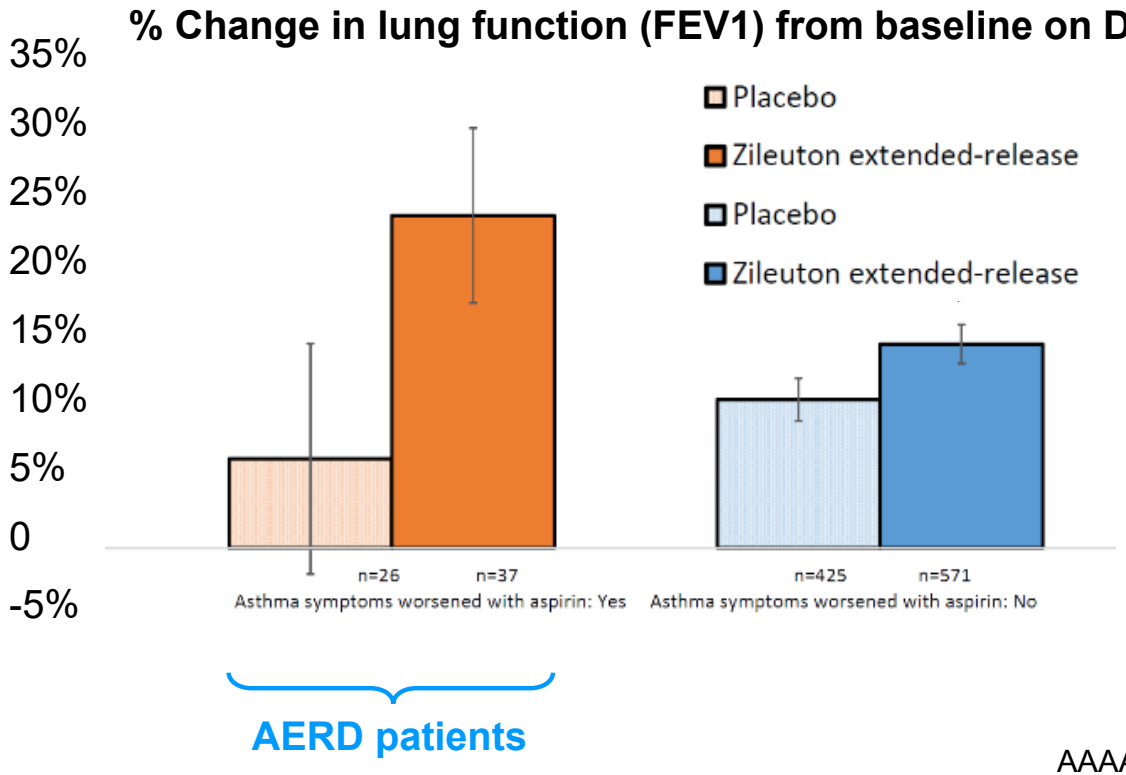
Ta and White, JACI IP, 2015 (190 patients)

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

➢ *Very useful for GI symptoms during aspirin reaction*

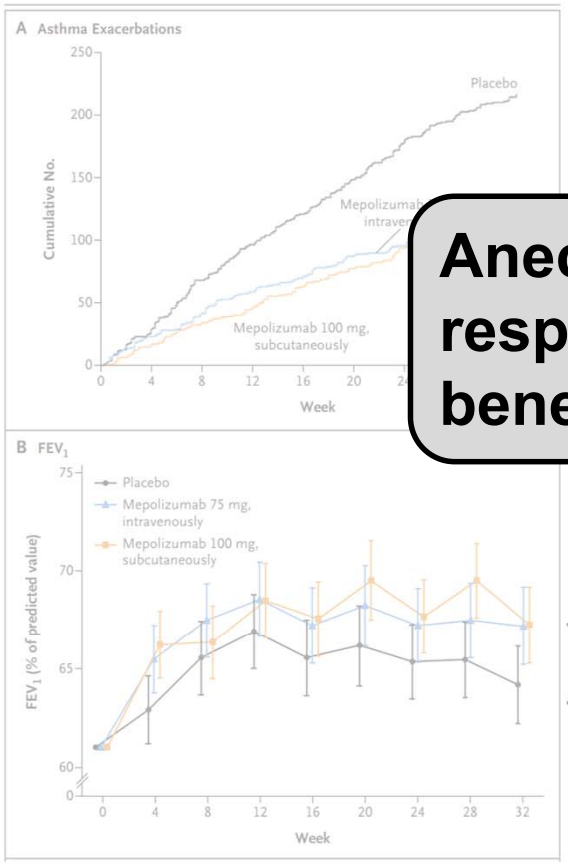
Zileuton is more effective in patients with AERD than in aspirin-tolerant asthma

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



AAAAI 2017 Poster L30

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



Ortega HG, et al. NEJM 2014

↓ 47-53% reduction in asthma exacerbations

↑ 98-100mL increase in FEV1

- 130-185mL increase in pts with eos ≥500 cells/μL

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

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

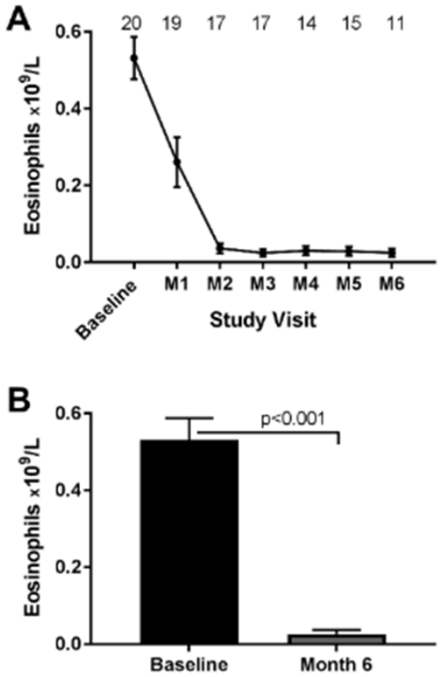
ase 3 nasal polyps

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

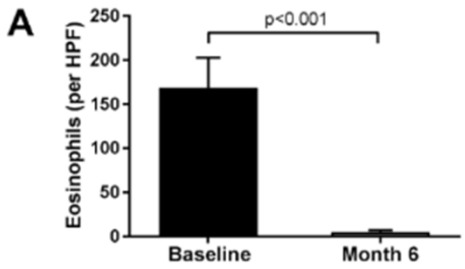
Han JK, et al. Lancet Resp Med 2021

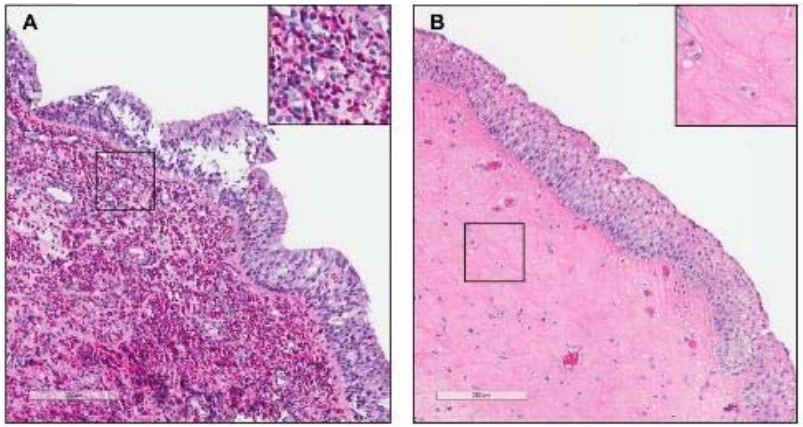
Dexpramipexole in CRSwNP – how important are eosinophils?

Blood eosinophils decrease

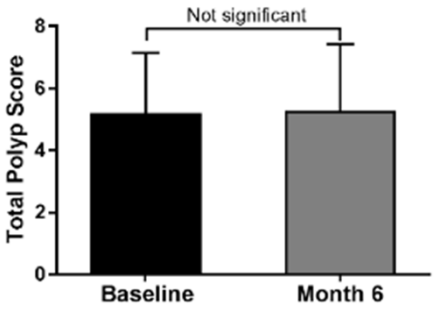


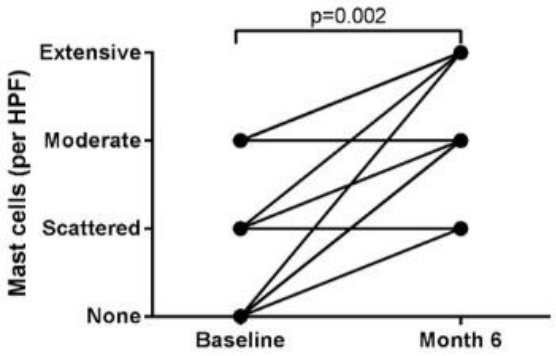
Polyp eosinophils decrease





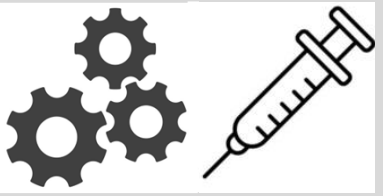
No improvement in polyp size



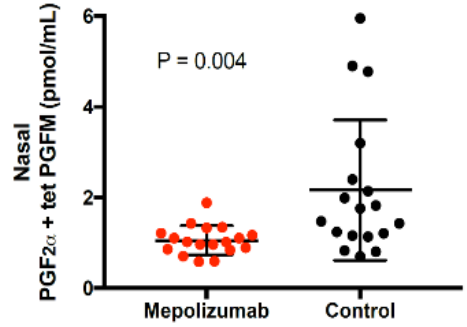


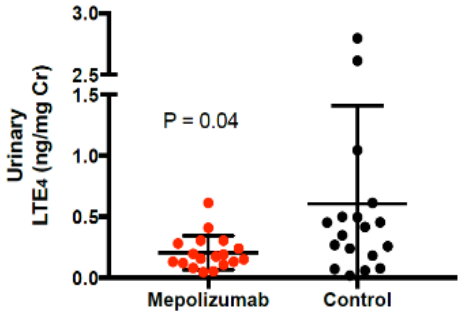
Laidlaw TM, et al. Laryngoscope. Feb 2019

Anti-IL-5 (mepolizumab for CRSwNP + AERD) does more than just decrease eosinophils



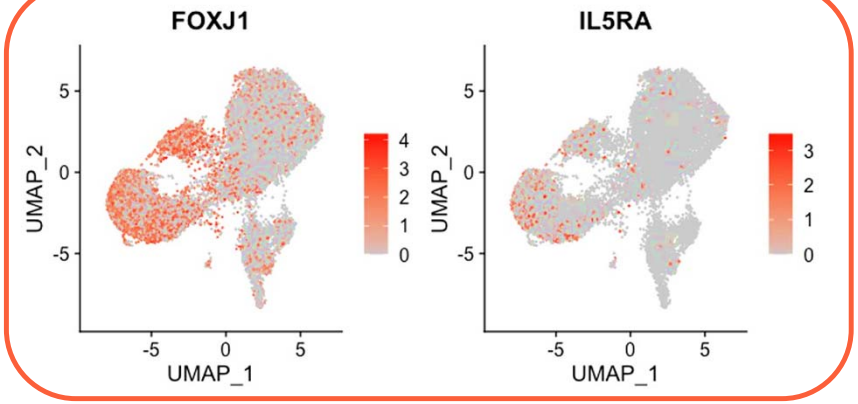
Nasal and urinary markers of <u>mast cell activation</u> decrease





Buchheit KM & Laidlaw TM, et al., 2021 JACI

<u>Ciliated nasal epithelial cells</u>



Role for <u>neutrophils</u>?

Mepolizumab and Benralizumab Reduce Eosinophilic Inflammation in Nasal Polyposis, Do Neutrophils Take Over?

"<u>Neutrophilic inflammation</u> in the sinus mucosa – presence of neutrophils and NETs – did not decrease after treatment but tended to be higher compared to untreated mucosal samples"

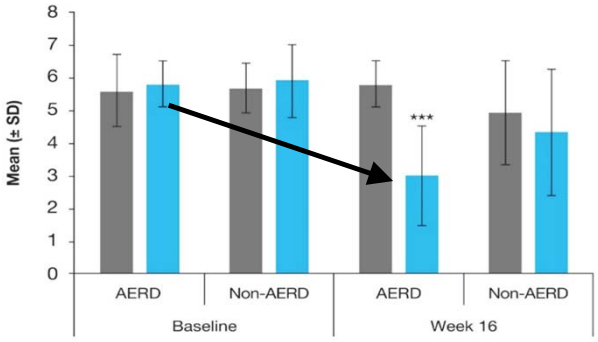
Delamarre T, et al., 2022 JACI Abstract/poster

Dupilumab in AERD (Phase 2)

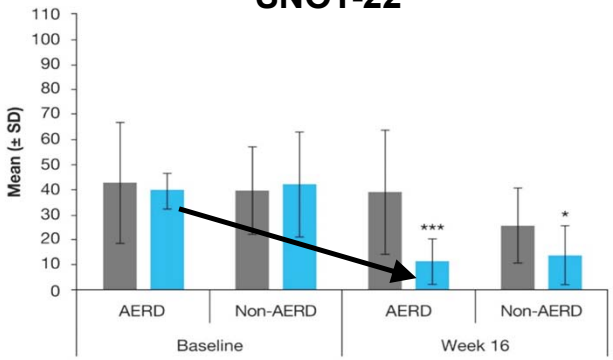
Re-analysis of Phase 2 study;
19/60 subjects had aspirin sensitivity

■ Dupilumab ■ Placebo

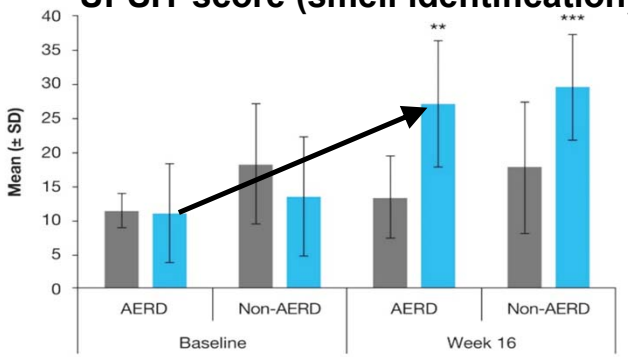
Nasal Polyp Score (0-8)



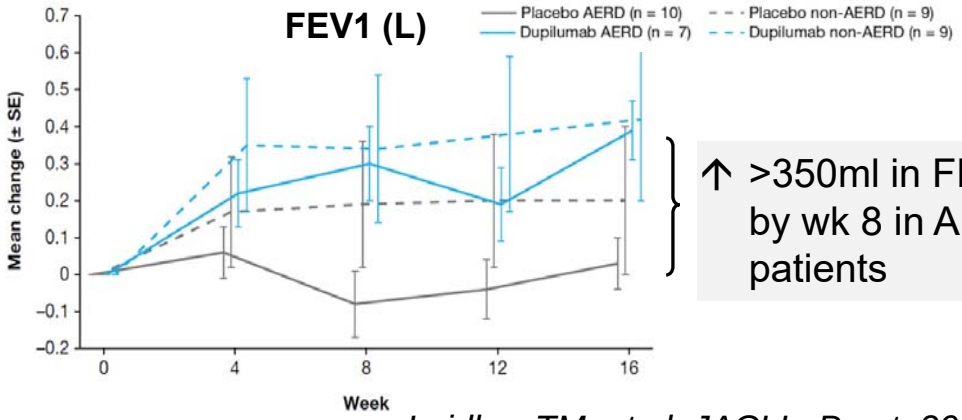
SNOT-22



UPSIT score (smell identification)



FEV1 (L)



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

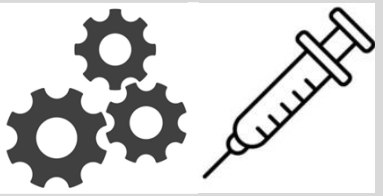
Laidlaw TM, et al. JACI In Pract. 2019.

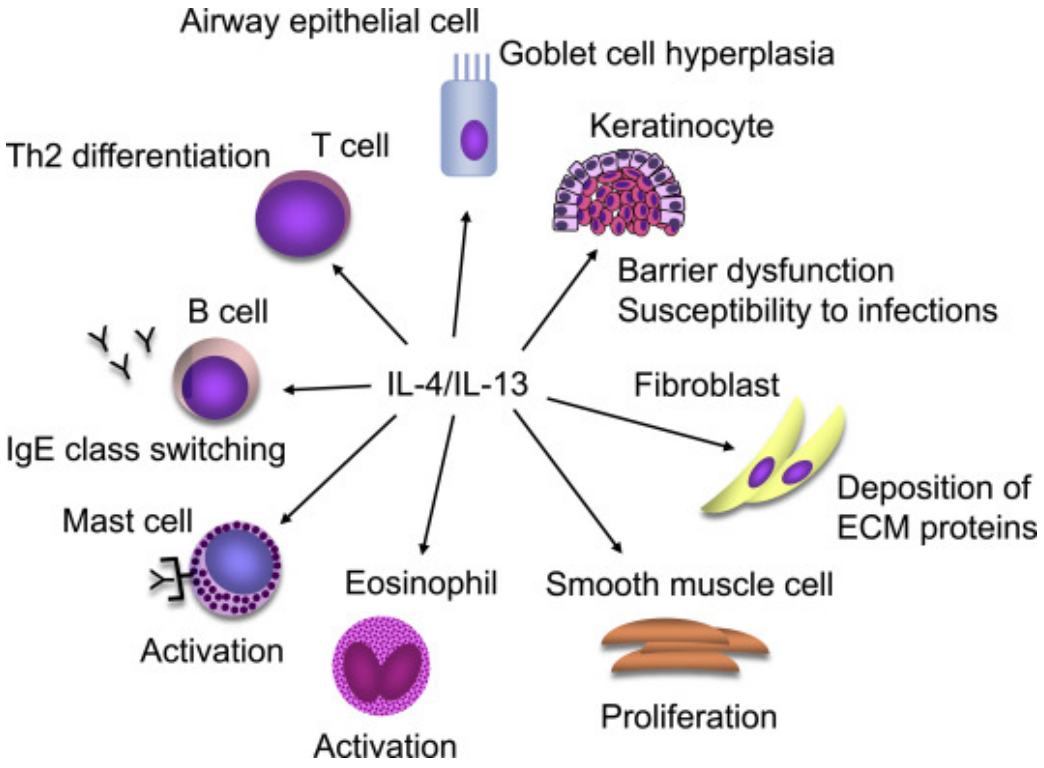
SINUS-52; Phase 3 nasal polyps

- 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

Bachert C, et al. Lancet 2019

Dupilumab (anti-IL-4Rα) targets many relevant cells





Matsunanga K et al. Allergology Int 2020

IL-4/13 ⇨ key cytokines that drive inflammation relevant to CRSwNP:

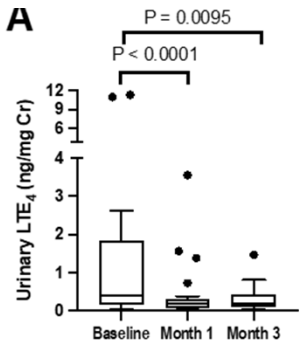
- **Goblet cell** hyperplasia/ **mucus** production
- Basement membrane thickening
- **Epithelial barrier** disruption
- **Eosinophil activation** in bone marrow
- **Mast cell** activation, ↑IgE receptor expression
- Inflammatory cell trafficking to tissues
- B cell class switching & **↑IgE production**

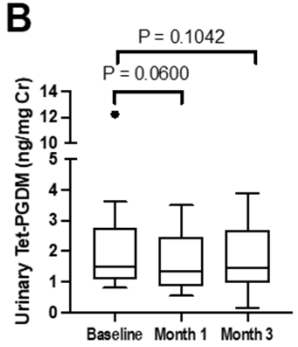
Mechanism of dupilumab-induced improvement in AERD? – pilot trial

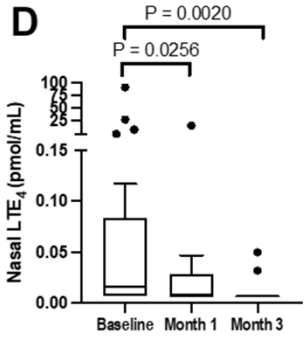
↓ cysLTs
Thought to be from MCs

NO Δ in PGD_2

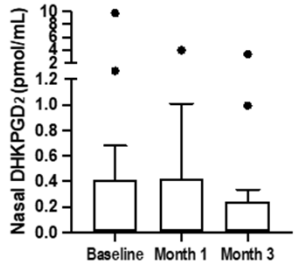
mast cell





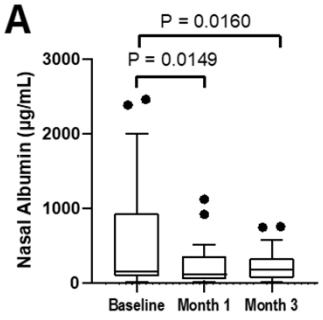


E NO Δ in tryptase



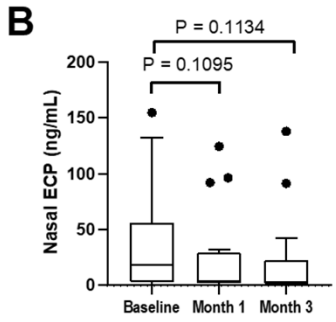
epithelium

↓ Nasal albumin

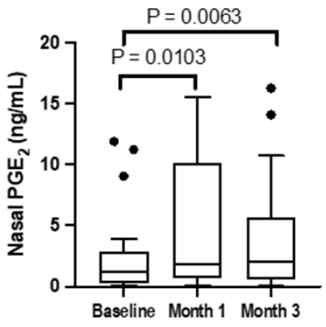


~~eosinophil~~

NO Δ in Nasal ECP



↑ Nasal PGE_2



Source of the PGE2…
- Macrophages?
- Fibroblasts?
- Epithelium?
- Granulocytes?

Buchheit & Laidlaw *et al.* JACI 2022

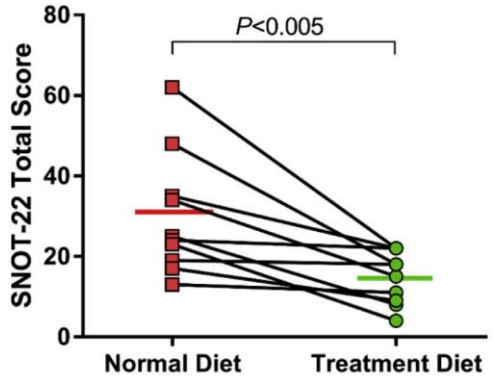
Diet to reduce omega-6 fatty acids (and increase omega-3) can decrease leukotrienes and improve symptoms in AERD

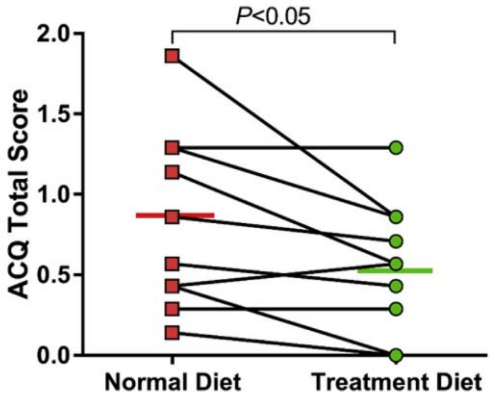
Good:

- 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

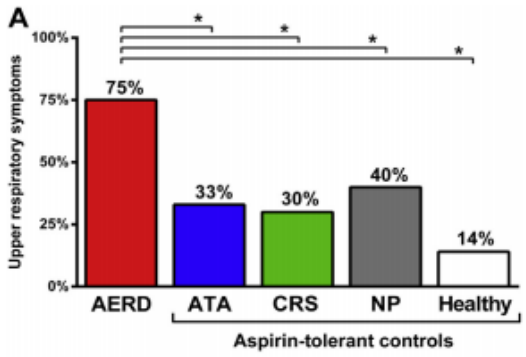




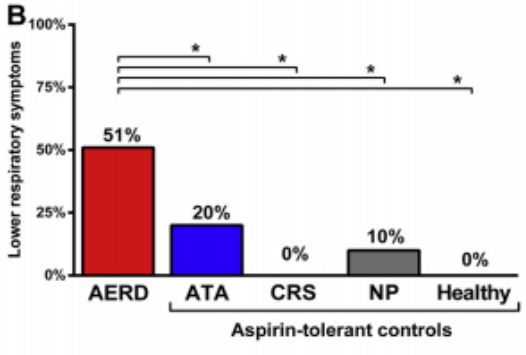
Schneider TR, Laidlaw TM. J Allergy Clin Immunol In Pract. 2018

Clinical clue: Respiratory reactions to alcohol

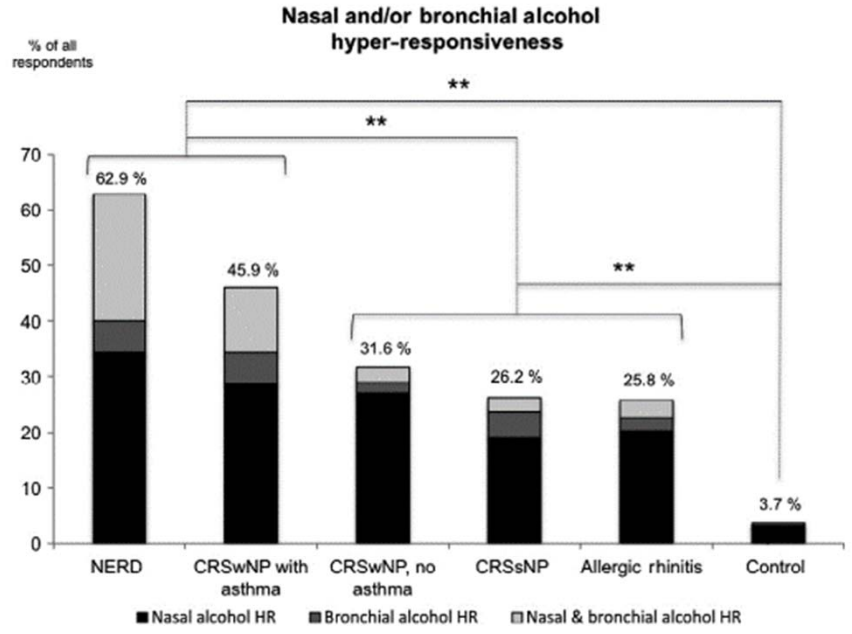
Upper respiratory reactions



Lower respiratory reactions



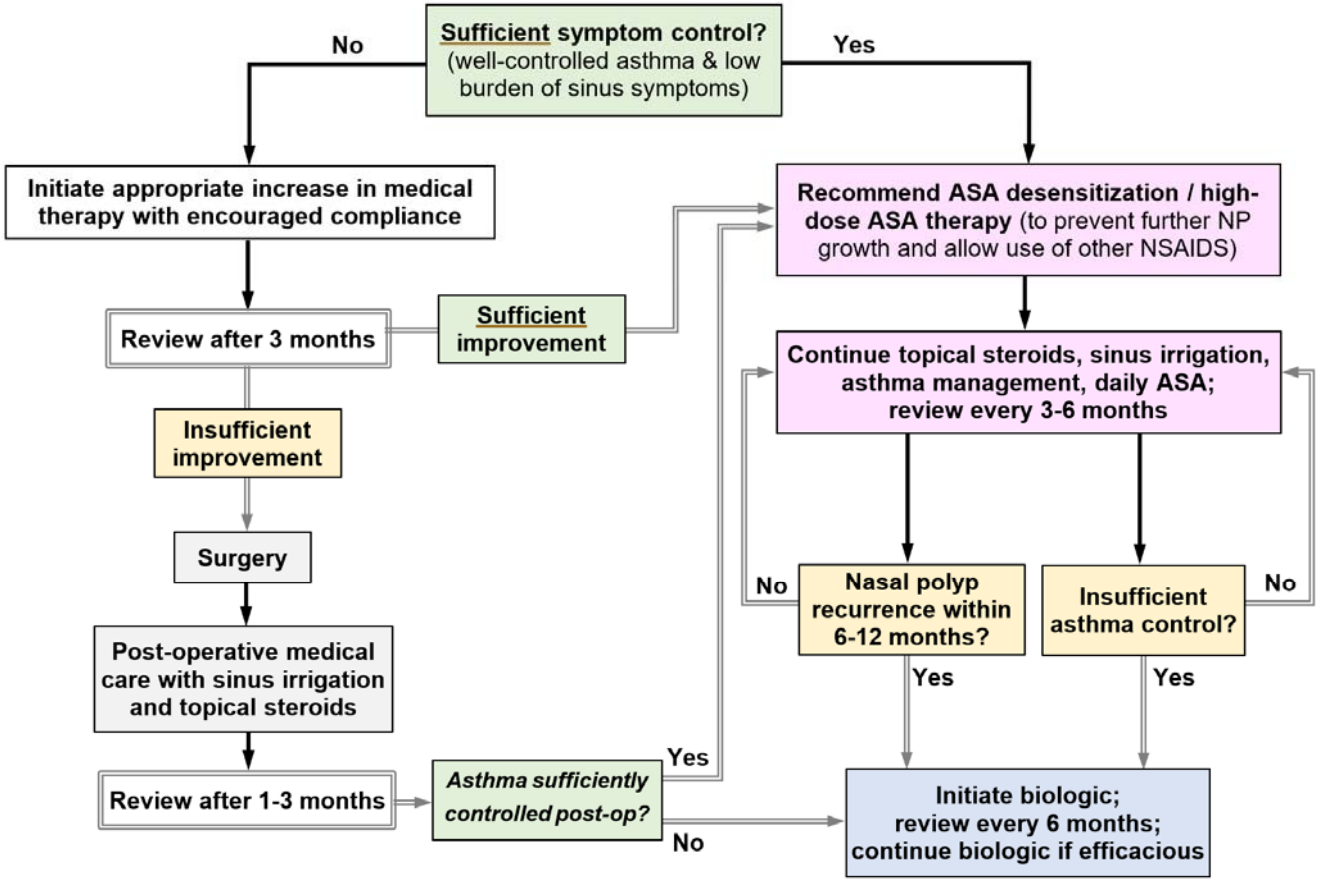
Cardet JC. JACI In Pract. 2014



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

Where biologics fit into AERD today



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

Summary – clinical points

- Triad: ask adult asthmatic patients about nasal polyps, sense of smell, COX-1 inhibitor tolerance
- Recognize classic reactions to aspirin & COX-1 inhibitors
- Understand role of leukotrienes and leukotriene modification in AERD
- Understand therapeutic role of new respiratory biologics

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HARVARD MEDICAL SCHOOL

Kathleen Buchheit, MD
AERD Center Co-Director

Cha Chen, MD
Allergy/Immunology Fellow

Regan Bergmark, MD
Rhinologist | ENT

Alice Maxfield, MD
Rhinologist | ENT

Rachel Roditi, MD
Rhinologist | ENT

Stella Lee, MD
Rhinologist | ENT

Jillian Bensko, PA-C
AERD Center

Aaqib Sohail, PhD
AERD Center

Laura Cho, BA
Laboratory Technician

Lily Li, MD
Allergist | NSAID Allergy

Kara VanGuilder, BA
Administration & Media

Tessa Ryan, BA
Research Coordinator

Alanna McGill, BA
Research Coordinator

Marie Lundberg, MD
Rhinologist | ENT

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