

BRIGHAM HEALTH



BRIGHAM AND
WOMEN'S HOSPITAL

Aspirin-exacerbated respiratory disease: Diagnosis and treatment

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



Mass General Brigham

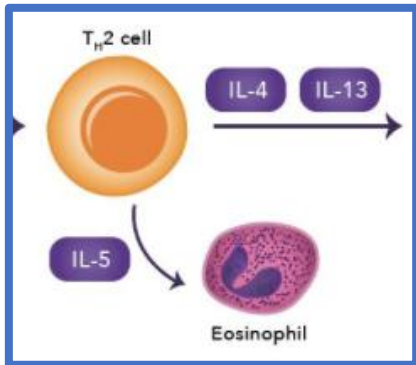
Conflict of Interest Disclosure

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

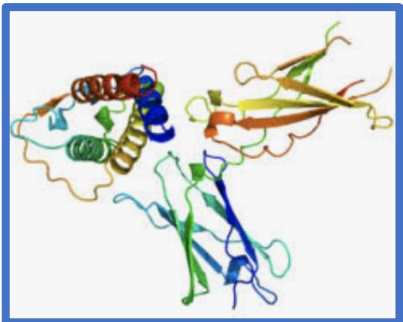
Objectives



Review the clinical presentation of aspirin-exacerbated respiratory disease (AERD)



Understand the pathophysiology of AERD as it relates to therapeutic options



Review updates in AERD diagnosis and management

Case AERD = 32 year-old “TB”

- Childhood → healthy, no asthma or allergies
- 18 yo → asthma, started on montelukast and ICS
- 19 yo → “really bad cold” and persistent nasal congestion
- 20 yo → continued congestion, lost sense of smell and taste, saw ENT surgeon, was “full of polyps”, had 1st polyp surgery (great improvement!), but polyps returned in 3 months
- 21yo → **ibuprofen** – 2 h later sneezed, chest tightness, wheezing
 - → 3 mo later **ibuprofen** – to ER for IV steroids and EpiPen
 - → 6 months later took **naproxen** – same reaction
- 22 – 31 yo → 4 additional polyp surgeries, polyps recurrence each time
- Now → Inhaled steroids, montelukast, steroid sprays, loratadine, albuterol 3-4 days/wk, no sense of smell, oral corticosteroids for sinusitis 2-3 times a year, polyps are back

AERD presents with a stereotyped pattern and common phenotype

Classic Triad:



Asthma



Nasal Polyps (severe and recurrent)



Respiratory reactions to COX-1 inhibitors

- Not IgE-mediated allergy to aspirin¹
- Not Mendelian inheritance²
- Not due to (known) environmental trigger³
- Almost always adult onset⁴

How common is it?

- 7% of adults with asthma
- 14% of adults with severe asthma
- 10 - 16% of adults with asthma+polyps
- ~ 1.5 million patients in U.S.⁵

¹Johns and Laidlaw, *Am J Rhinol Allergy* 2014

²Cahill and Laidlaw, *Am J Resp Cell Mole Biol* 2016

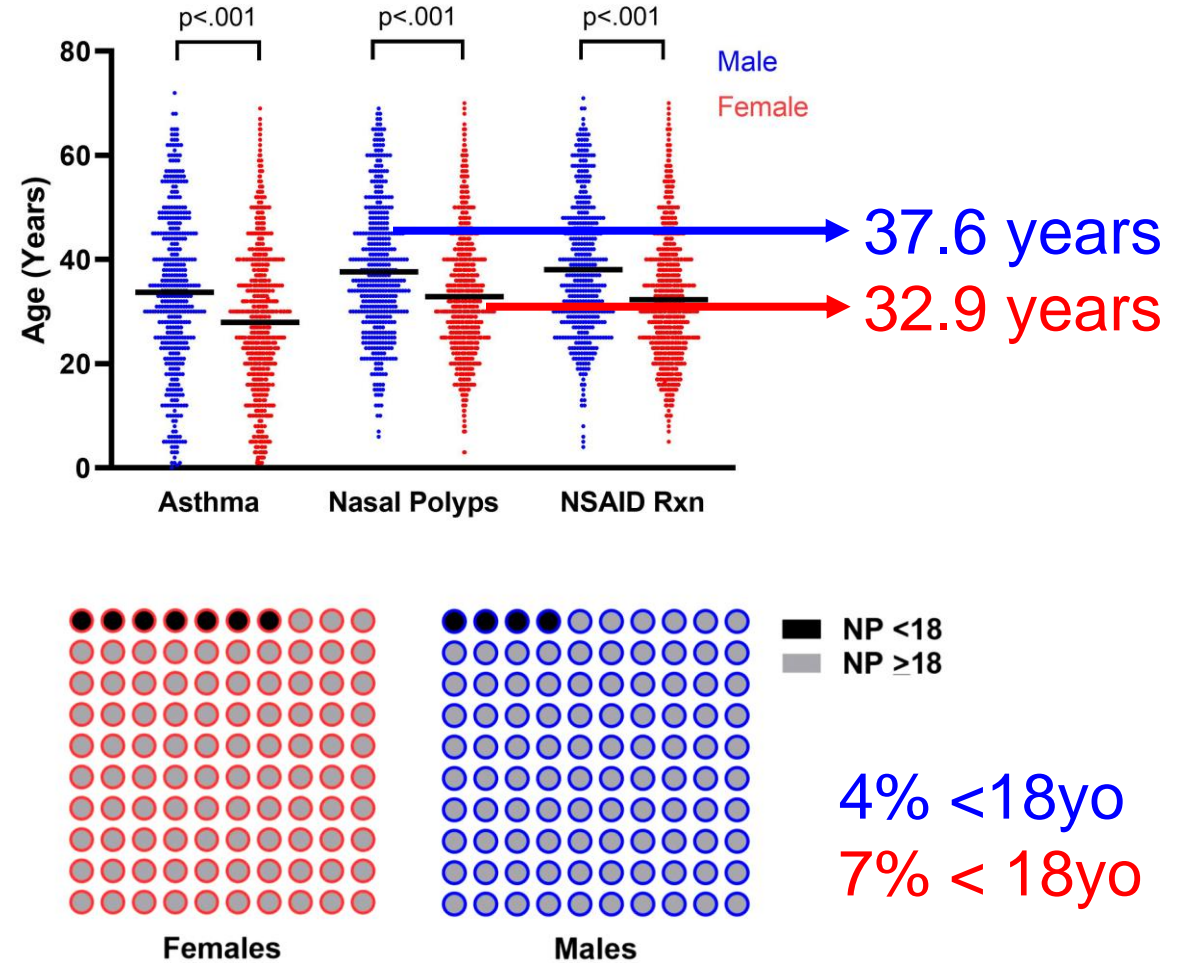
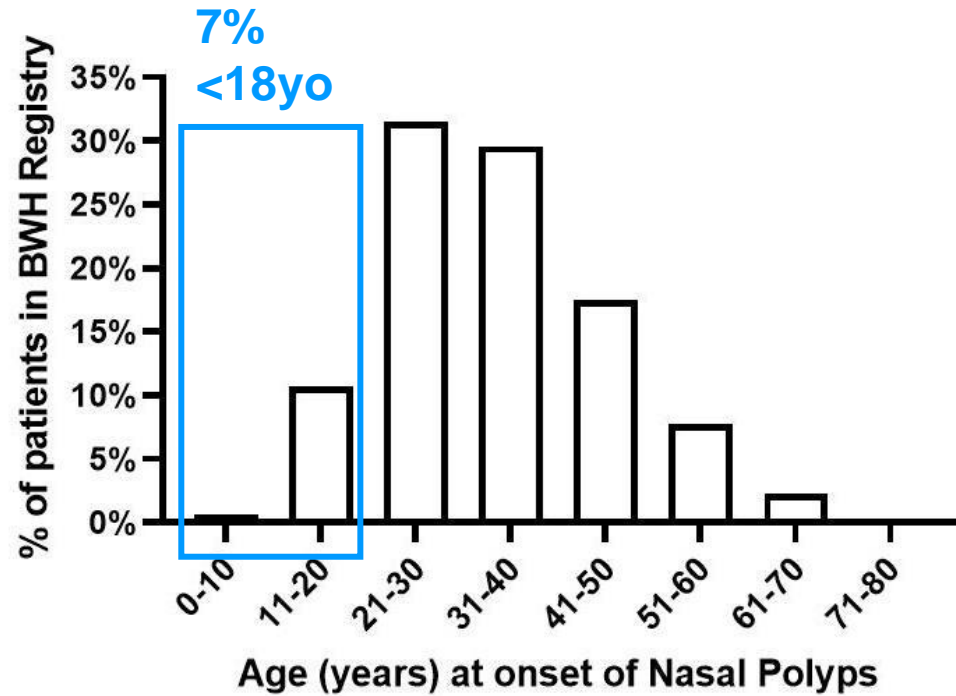
³Chang and Stevenson, *Ann Allergy Asthma Immunol* 2012

⁴Tuttle and Laidlaw, *JACI:IP* 2016

⁵Rajan and White, *JACI* 2015, *Meta-analysis*

Age and gender: >2000 patients at BWH AERD Center

Largely adult-onset disease...

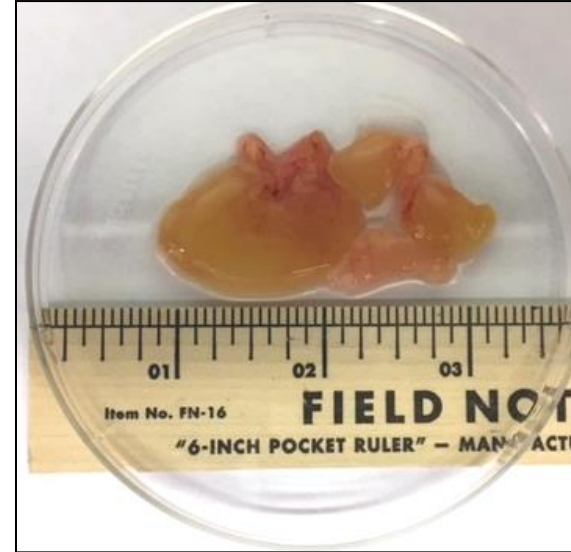


Surgery is a key treatment modality for AERD

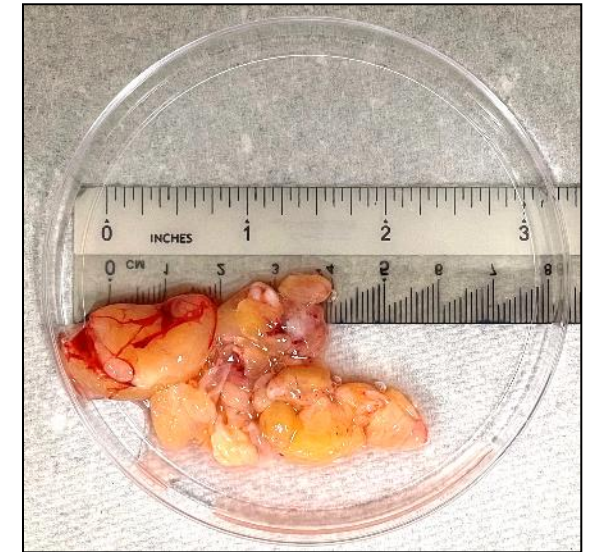
Typical appearance of polyps on rhinoscopy, and can be very large



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

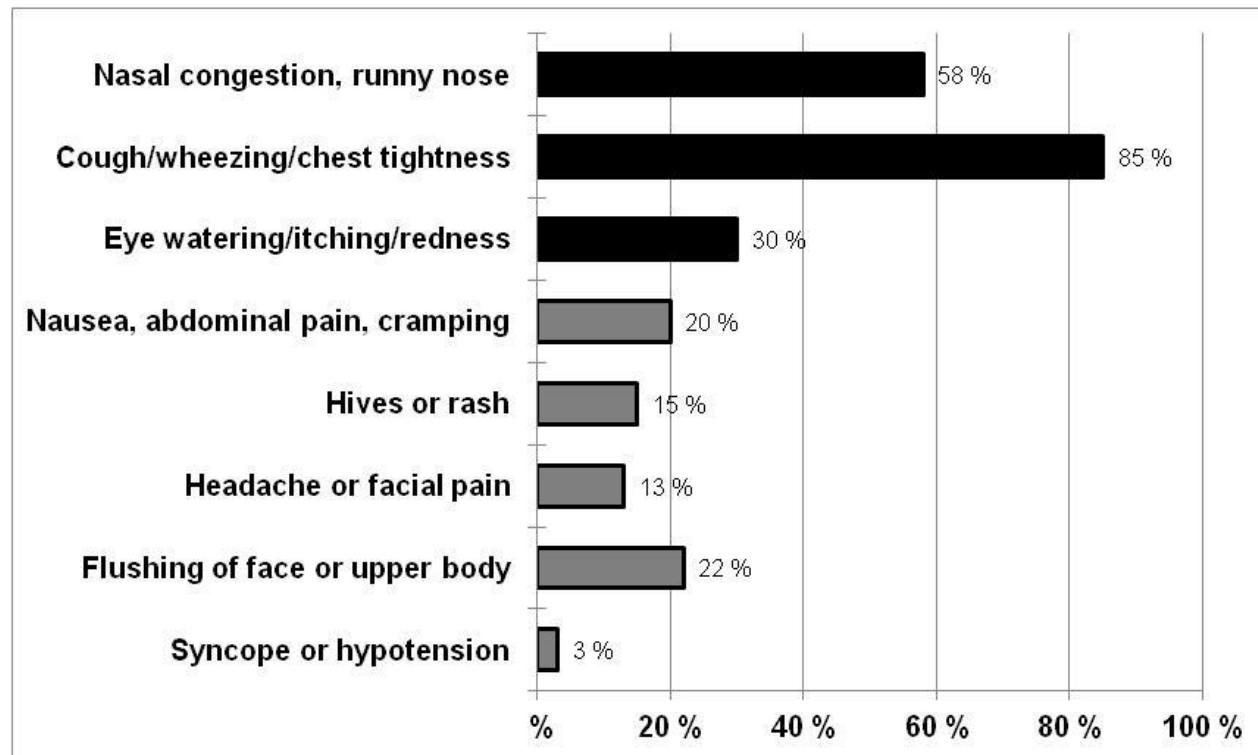
History of polyp surgery:

- 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.

AERD: Reactions to Aspirin/NSAIDs

Classic reaction:

- Bronchoconstriction = wheezing, cough, fall in FEV₁
- Nasal/ocular symptoms = sneezing, congestion, headache/facial pressure, rhinorrhea, eye tearing, eye redness/swelling

Less common:

- Rash, urticaria, angioedema
- Abdominal pain, nausea, vomiting¹

- Average time to reaction is ~60 minutes after aspirin exposure and doses of ≤ 162 mg of aspirin elicited reaction in >95% of patients with AERD.²

*3 – 6% of patients react to ≤ 650 mg acetaminophen³

*34% of patients react to > 1000 mg acetaminophen⁴

*Patients tolerate selective COX-2 inhibitors (**pain control**)

¹Cahill KN, et al. JACI 2015; 135:245-52.

²DeGregorio GA, et al. JACI 2019; 137(4):1174-1180.

³Szczeklik A, et al. JACI 1977; 60:276-284.

⁴Settipane RA, et al. JACI 1995; 96:480-85.

Tolerance of COX-2 inhibitors AERD

Black Box Warning: “Celecoxib is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.”

Nine Publications from 6 groups have proven safety of COX-2 inhibitors in AERD.

1 case report of etoricoxib-induced respiratory reaction in AERD.

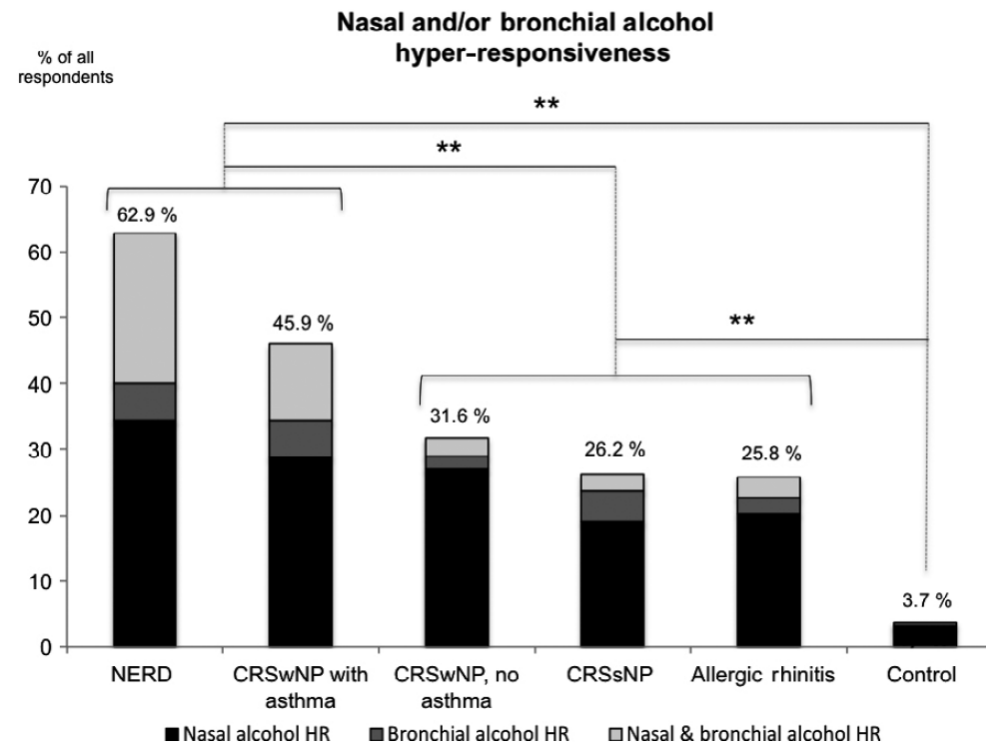
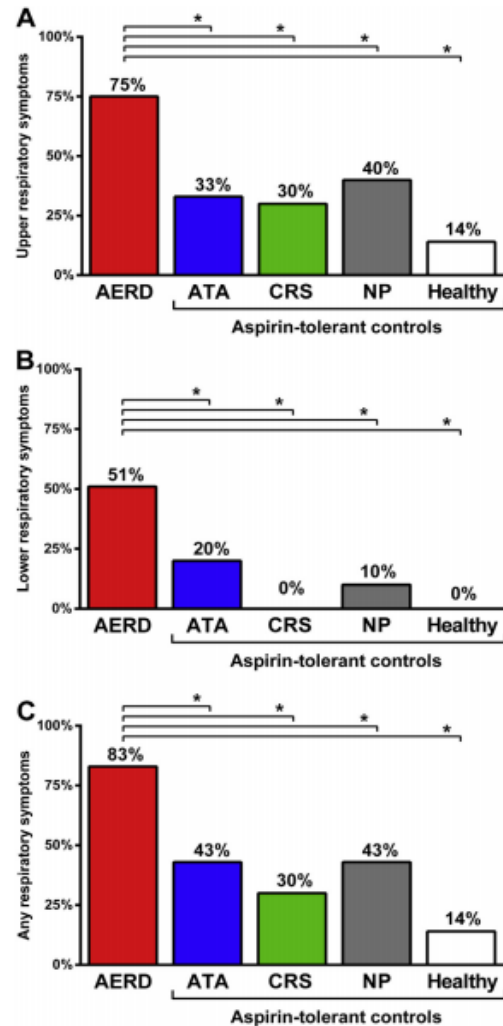
Stevenson DD et al. JACI 2001
Woessner KM et al. Ann Allergy Asthma Immunol. 2004
Woessner KM et al. Arthritis Rheum 2002
Gyllfors BG et al. JACI 2003
Yoshida S et al. JACI 2000
Micheletto C et al. Euro Annals of Allergy and Clin Immunol 2006
Celik G et al. J Asthma 2005
Martin-Garcia C et al. Journal of Investig All and Clin Immunol. 2003
Szczeklik A et al. Clin Exp Allergy 2001
Koschel D et al. Allergy 2008

Tricks to make AERD diagnosis

What if you feel like it could be AERD, but patient says “no” to the “Do you have any problems when you take aspirin, ibuprofen, or naproxen?” question:

- ? Patient has not taken aspirin/NSAIDs in a long time
- ? Patient is on 81mg aspirin daily (already desensitized)
- ? Patient is on montelukast or zileuton
- ? Patient is so ridiculously stuffed up with polyps at baseline that they couldn't even tell if got worse.

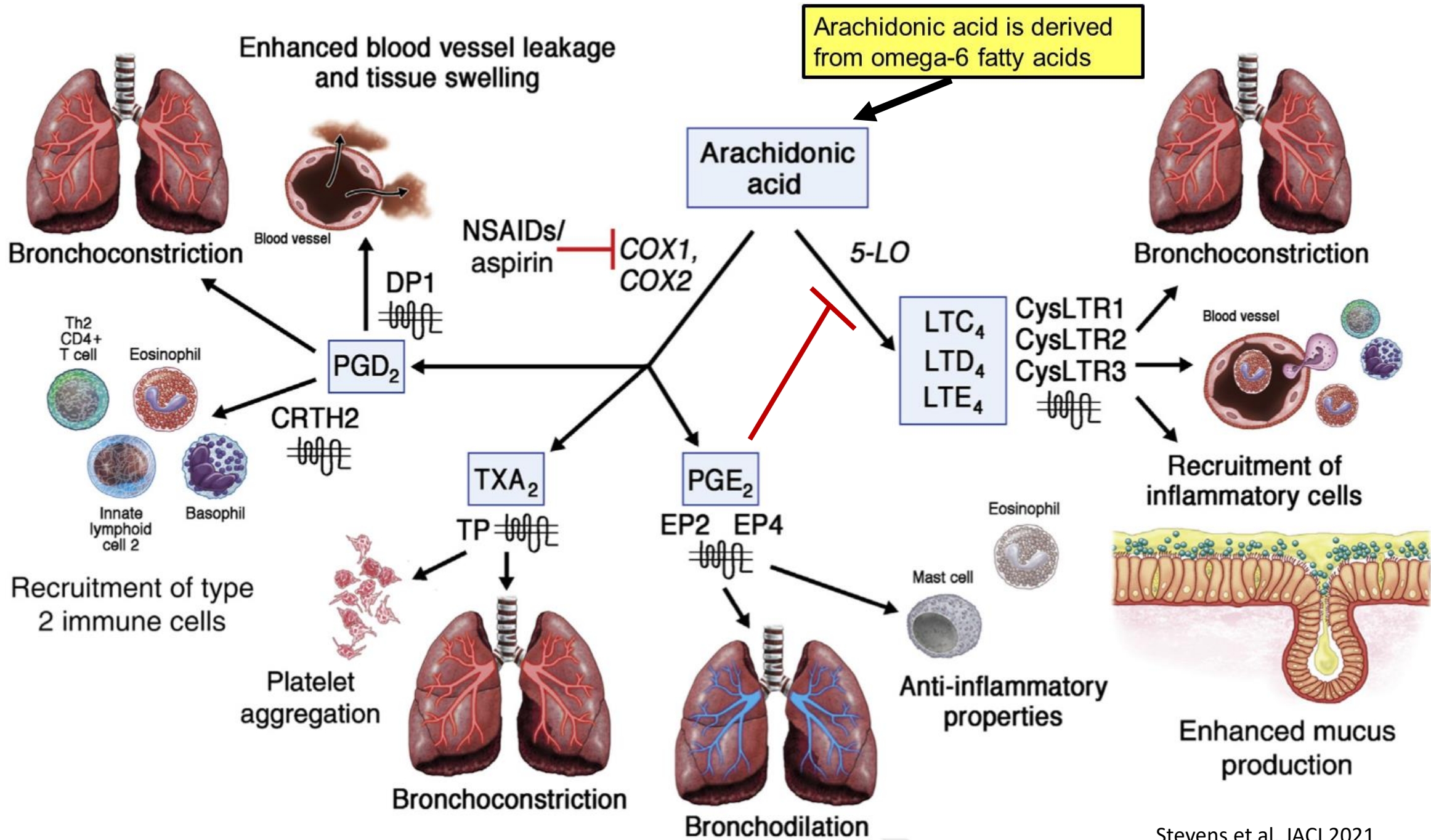
Clinical clue: Respiratory reactions to alcohol



De Schryver E. Clin&ExperAll 2016

AERD: Pathophysiology

1. Dysregulated cysteinyl leukotrienes (CysLT)
 - Excessive basal CysLT generation
 - Increase CysLT generation upon COX-1 inhibition
 - Airway hyperresponsiveness to CysLTs
 - Baseline levels correlate with severity of aspirin-induced asthma attack
2. Mast cell activation
 - Prostaglandin (PG) D₂, histamine, tryptase, leukotrienes
 - At baseline
 - During aspirin reaction
 - Inhibitors of mast cell activation modify reactions to aspirin
 - Driven in-part by innate type 2 cytokines, tissue immunoglobulin (Ig) E



Summary: Clinical/mechanistic points

- Triad: ask all adult asthmatic patients about nasal polyps, sense of smell, and COX-1 inhibitor tolerance
- Respiratory reactions with all COX-1 inhibitors, some patients also sensitive to acetaminophen, but **selective COX-2 inhibitors are tolerated**
- Disease of dysregulated leukotrienes and mast cell activation → Activation of effector cells including Th2 cells, ILC2s, eosinophils, basophils, and neutrophils/platelets

Next: Updates in management

Updates in management of AERD

- Aspirin desensitization
- Leukotriene modification
- Biologic therapy
 - Omalizumab (anti-IgE)
 - Anti-interleukin(IL)-5/IL-5R α
 - Dupilumab (anti-IL-4R α)
 - Tezepelumab (anti-TSLP)
- Dietary intervention





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

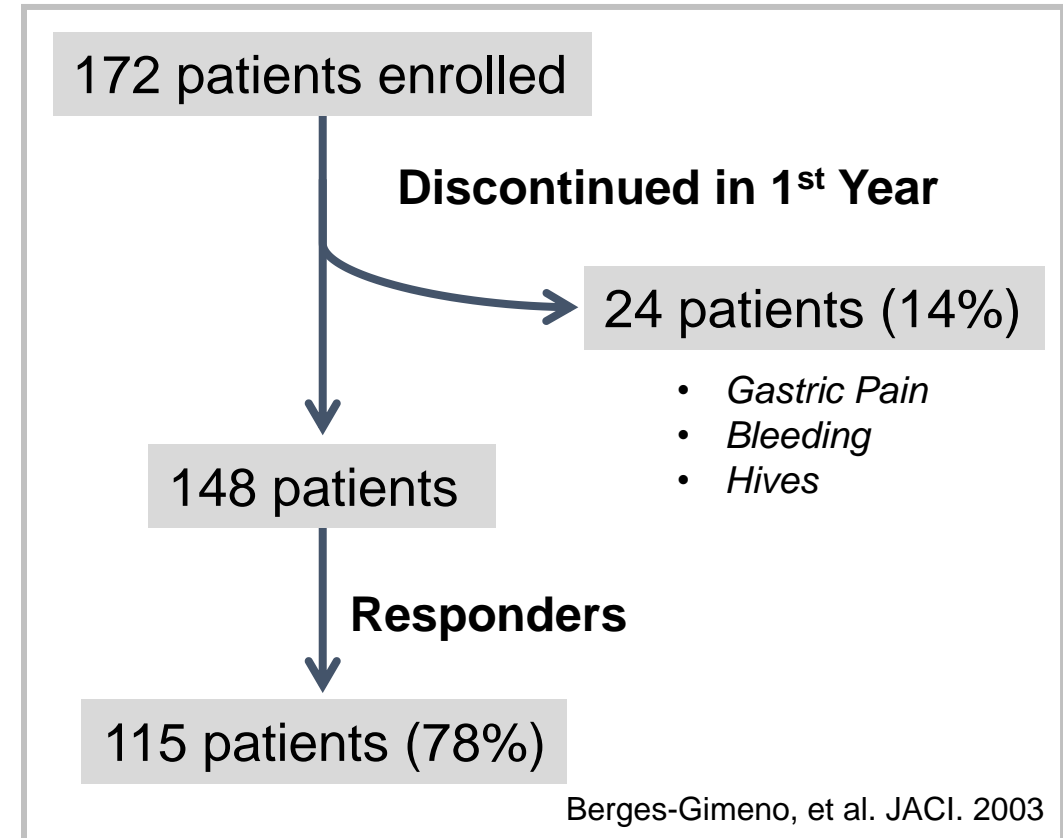
Mizankowska-Mogilnicka, et al. JACI 2014

When to do aspirin challenge?

- **Preferably before surgery.**

When to desensitize?

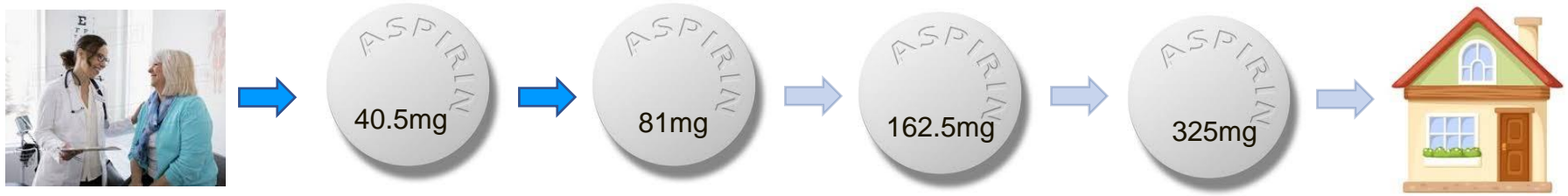
- **Preferably after surgery.**



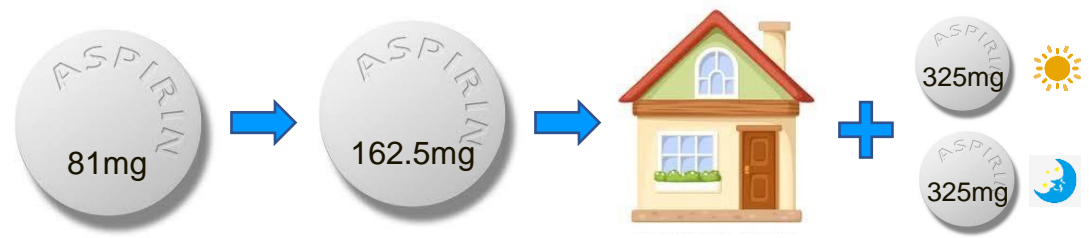
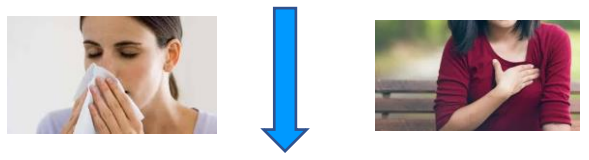
Aspirin desensitization and high-dose oral aspirin (to treat) - PROTOCOL

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

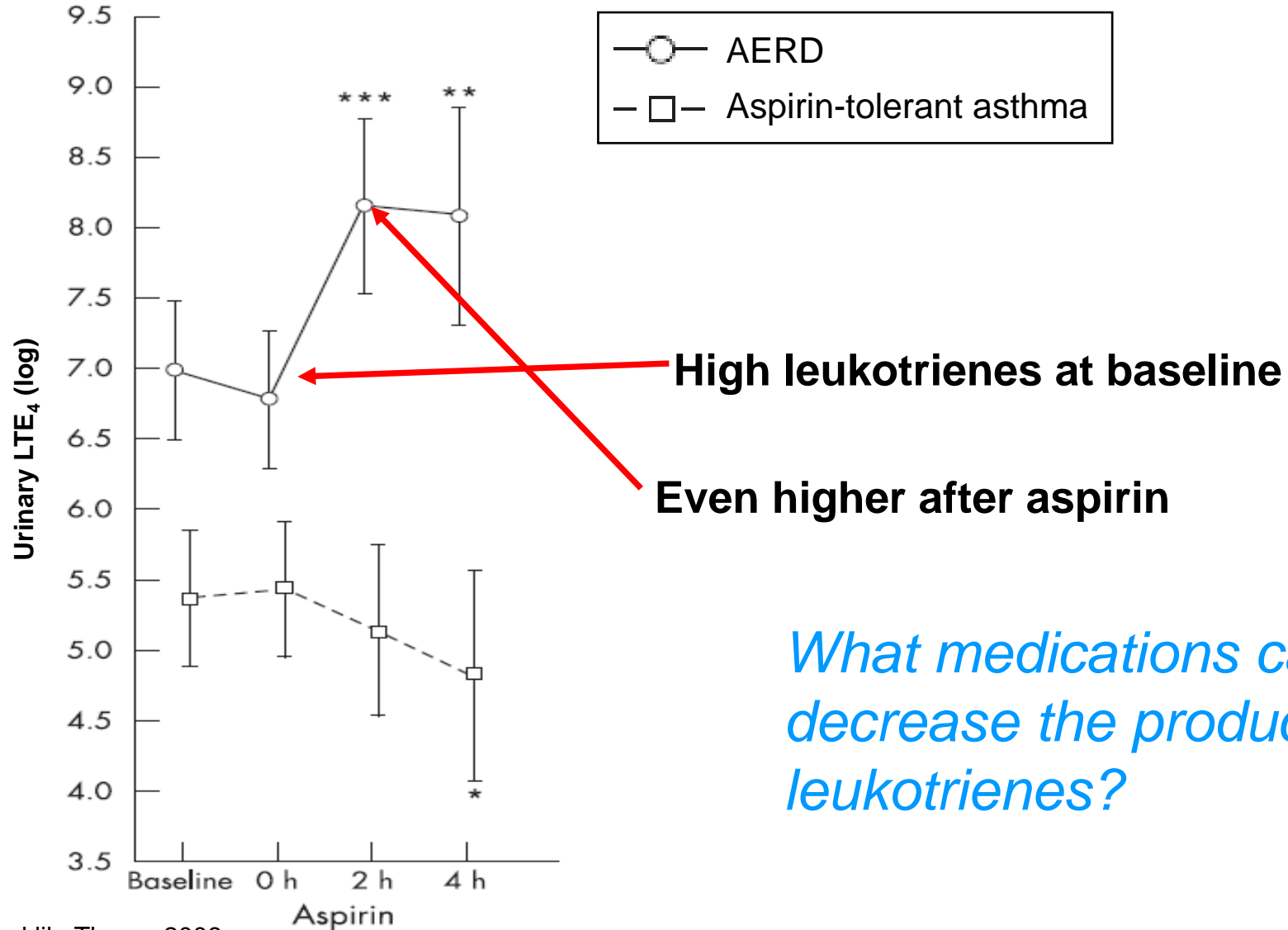
Challenge



Provocation of symptoms



Leukotrienes are dysregulated in AERD



What medications can we use to decrease the production or effects of leukotrienes?

Use of leukotriene-modifying medications in AERD

- **Zileuton** (5-LO inhibitor) and **montelukast** (cysLT1 receptor antagonist) improve AERD symptoms at **baseline**

- **Zileuton:** ↑ FEV₁, improves smell, ↓ short acting beta agonist use

- Dahlen B, Szczeklik A et al. AJRCCM 1998

- **Montelukast:** ↑ FEV₁, improves nasal symptoms scores

- 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)

- **For aspirin desensitization:**

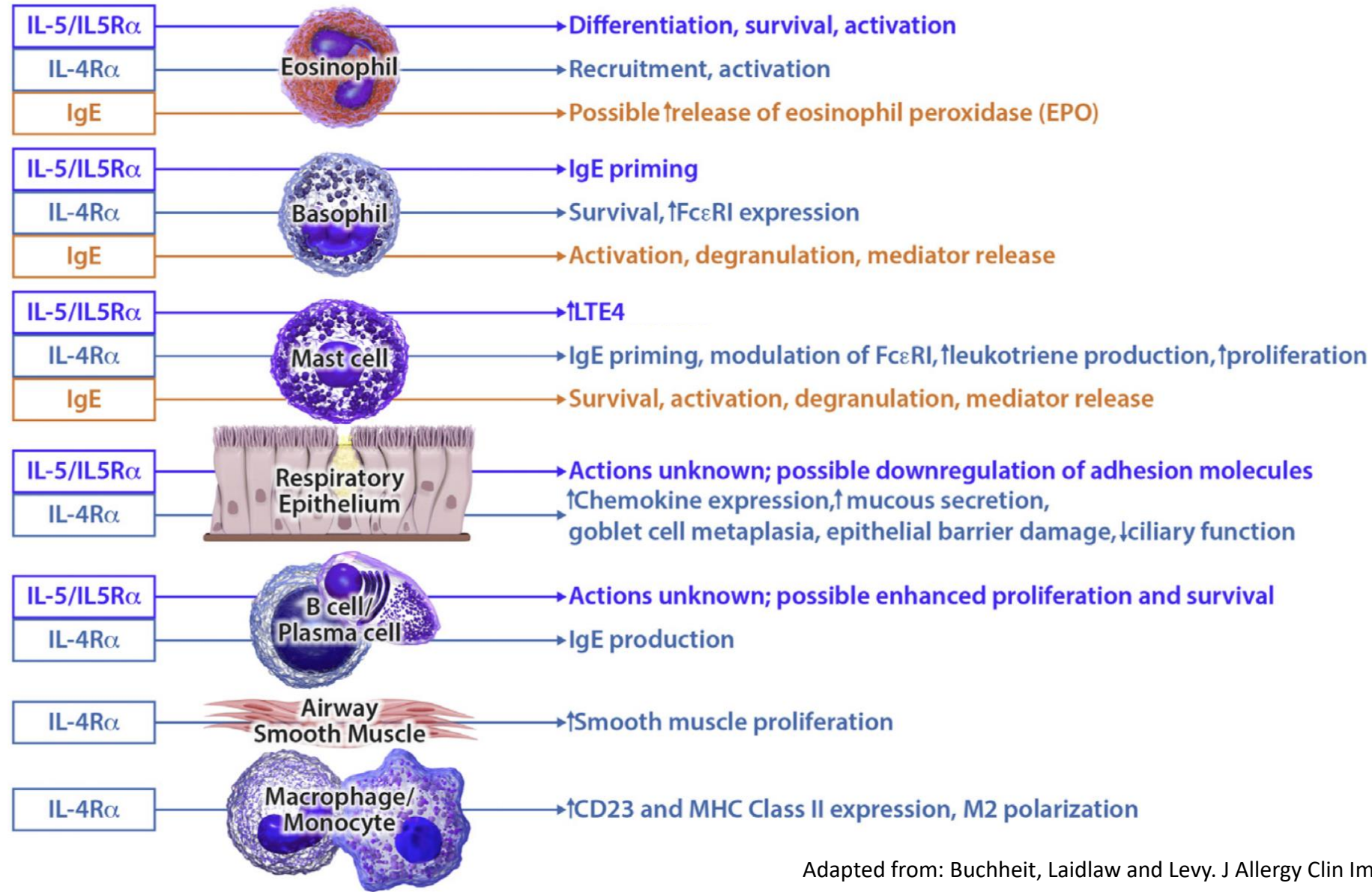
- **Montelukast: Blunts fall in FEV₁ = Safer desensitization**

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

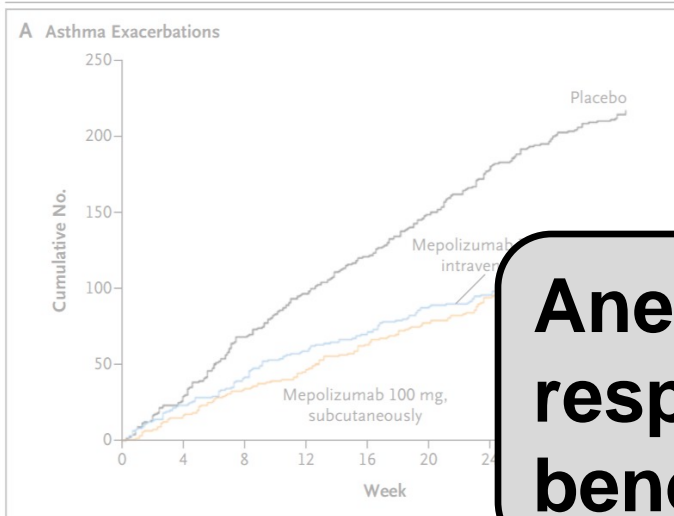
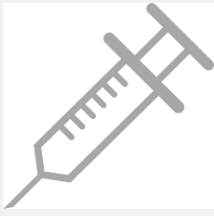
- **Zileuton: Can increase provocative dose or block reactions completely**

- *Useful for gastrointestinal reactions during desensitization*

IgE, IL-5, and IL-4R α : targets of currently available respiratory biologic medications for CRSwNP



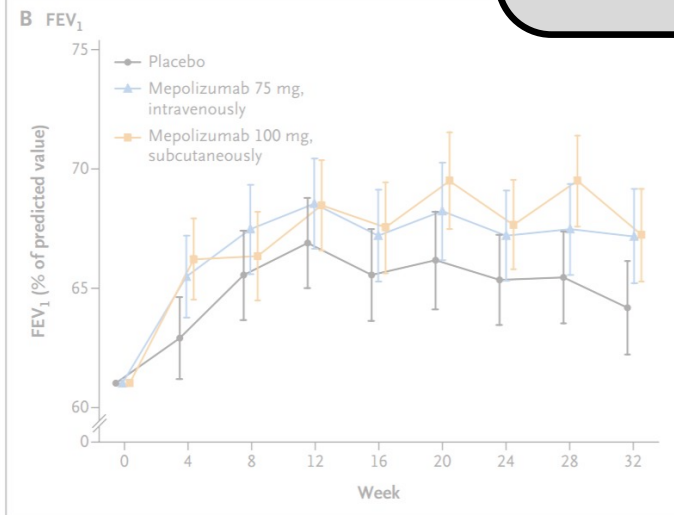
Mepolizumab (anti-IL-5) improves asthma control & lung function in eosinophilic asthma, reduces nasal polyp scores



↓ 47-53% reduction in asthma exacerbations

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

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



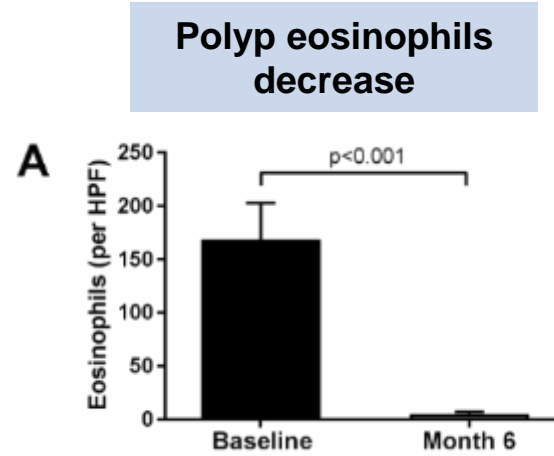
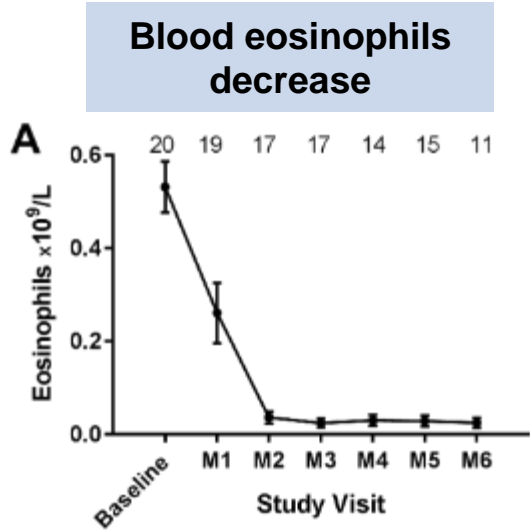
↑ 98-100mL increase in FEV1
• 130-185mL increase in pts with eos \geq 500 cells/ μ L

Phase 3 nasal polyps total score of 0.73 at 52wks

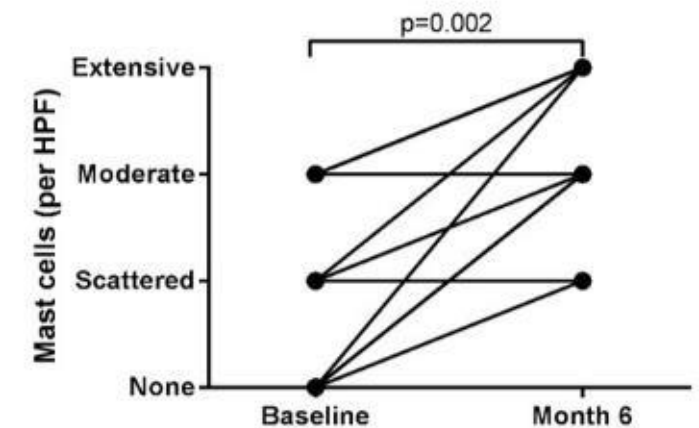
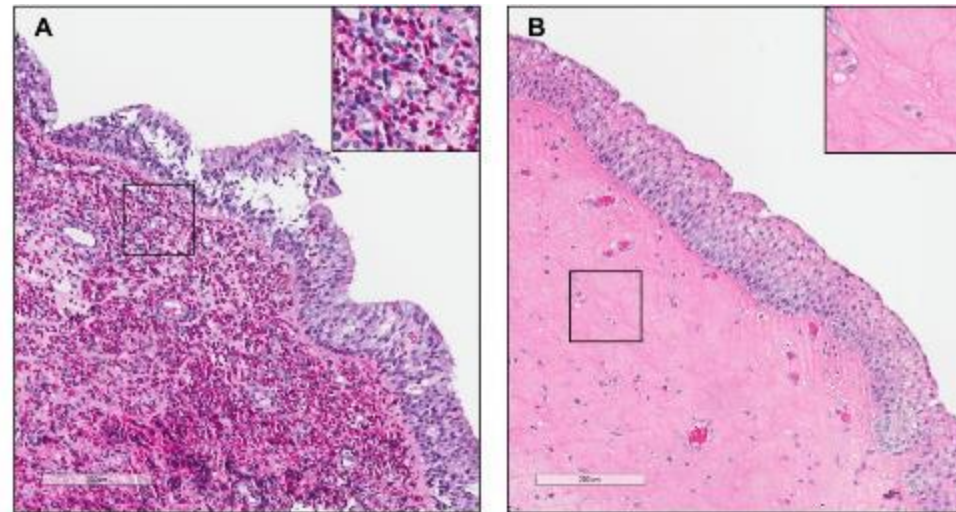
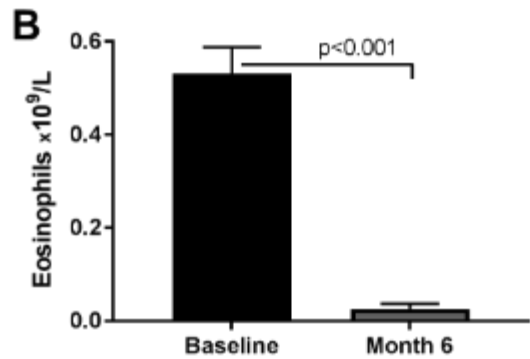
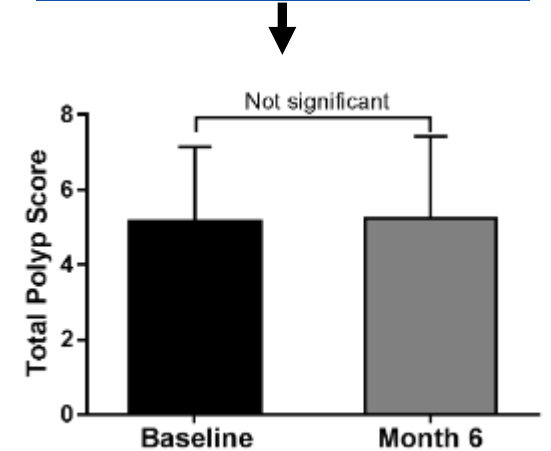
- No significant improvement in smell (UPSIT)
- 108 AERD patients
- ↓ NP score of 0.89 at 52wks

Han JK, et al. Lancet Resp Med 2021

Dexpramipexole in CRSwNP – how important are eosinophils?

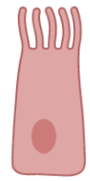
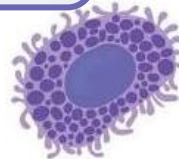
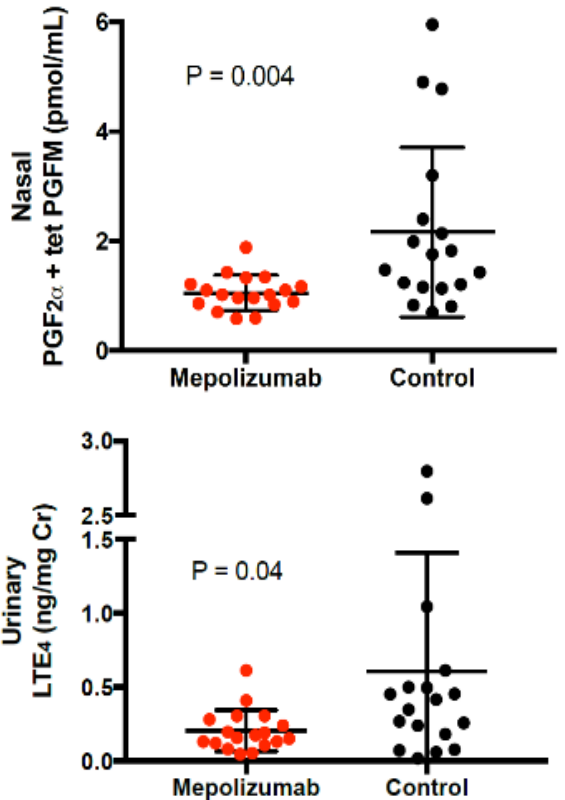


No improvement in polyp size

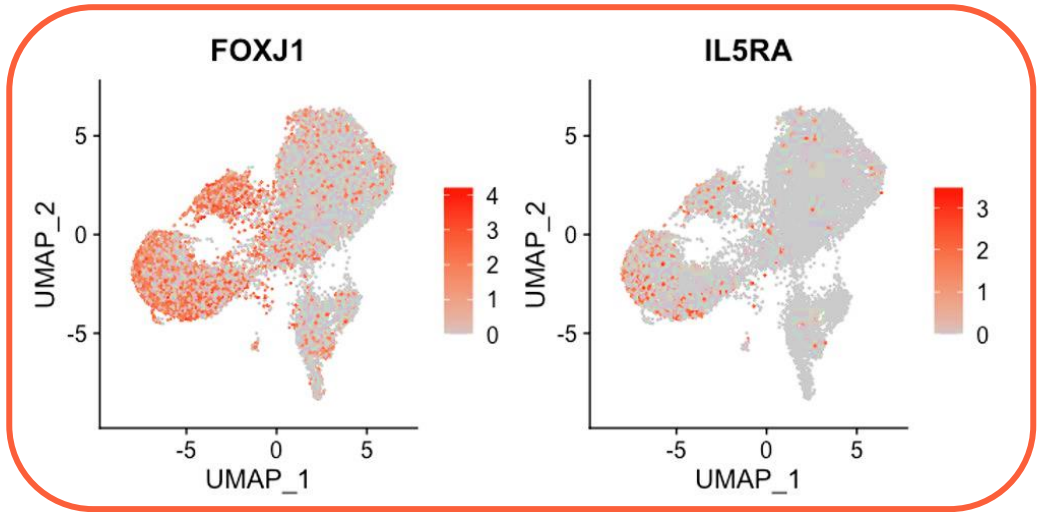


Anti-IL-5 (mepolizumab for CRSwNP + AERD) does more than just decrease eosinophils

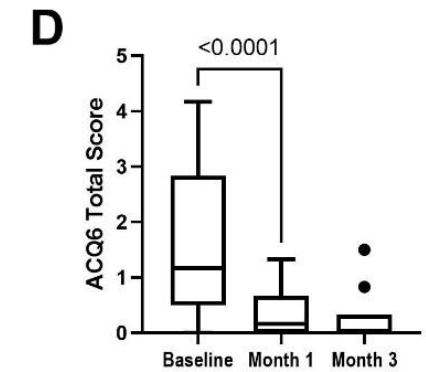
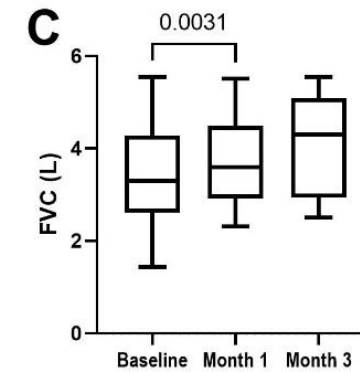
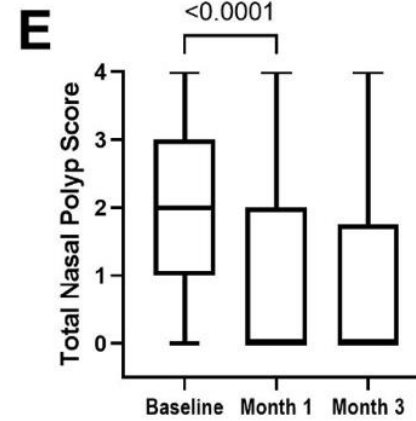
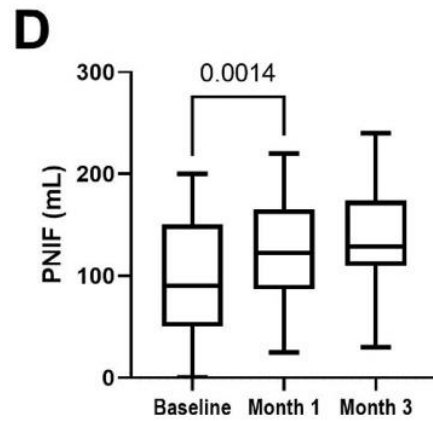
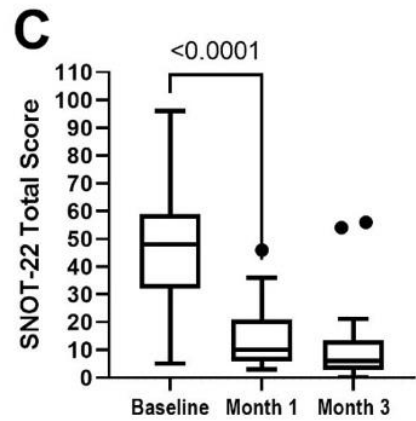
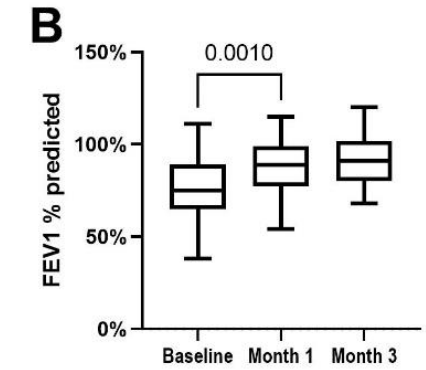
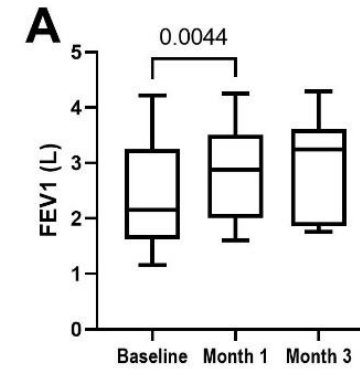
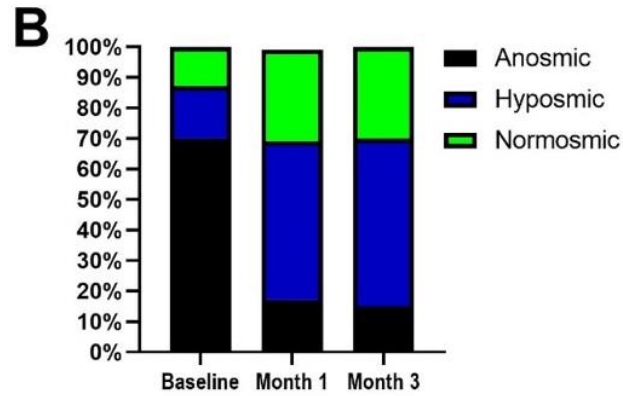
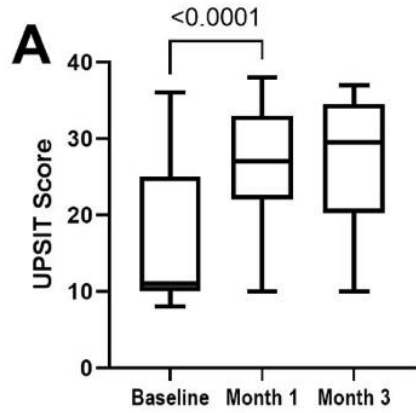
Nasal and urinary markers of mast cell activation decrease



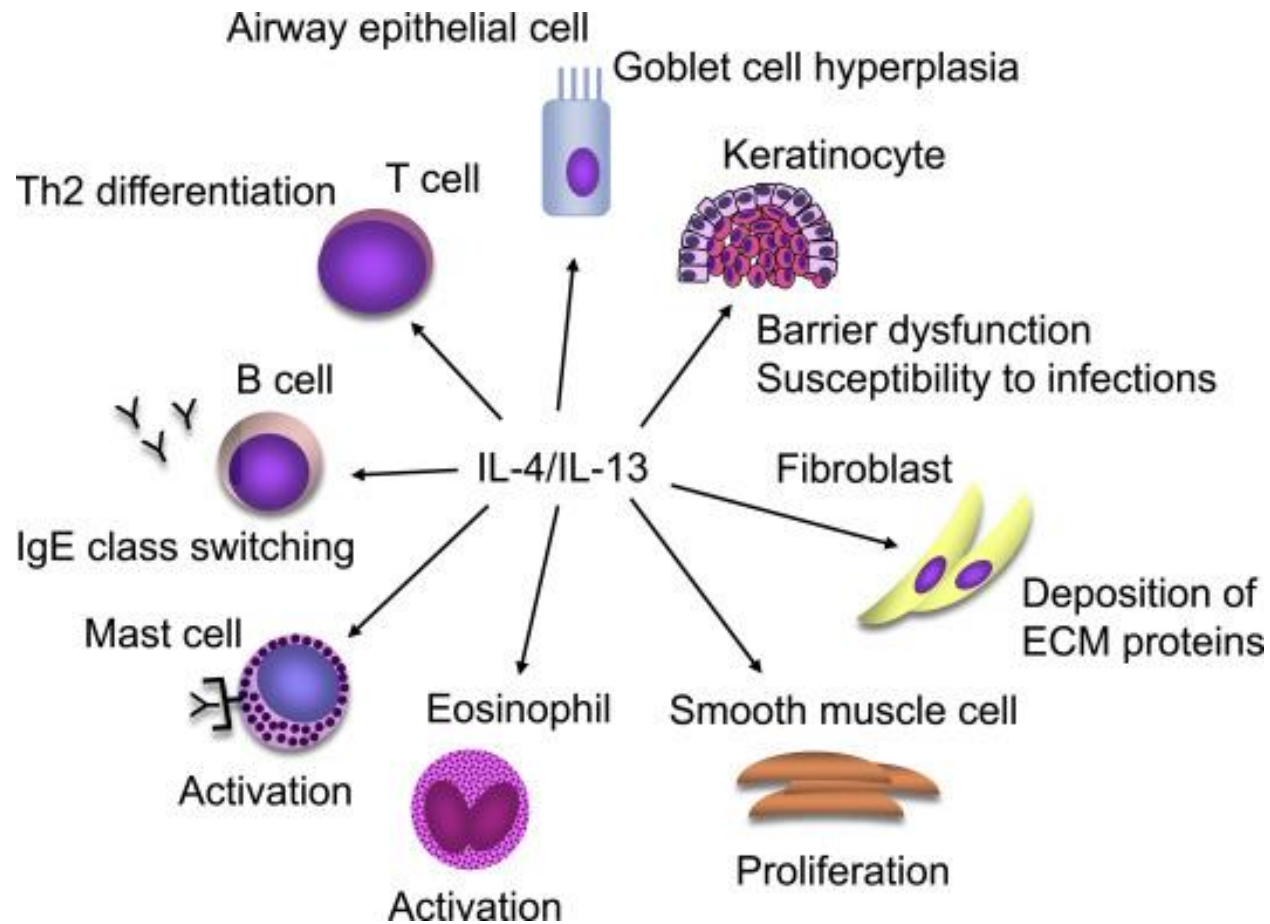
Ciliated nasal epithelial cells



Dupilumab-induced changes in clinical outcomes



Dupilumab (anti-IL-4R α) targets many relevant cells



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

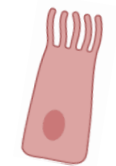
- **Goblet cell** hyperplasia/ mucus production
- Basement membrane thickening
- **Epithelial barrier** disruption
- **Eosinophil activation** in bone marrow
- **Mast cell** activation, \uparrow IgE receptor expression
- Inflammatory cell trafficking to tissues
- B cell class switching & \uparrow **IgE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

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



↓ cysLTs
Thought to be from MCs

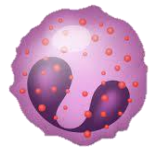
NO Δ in PGD₂



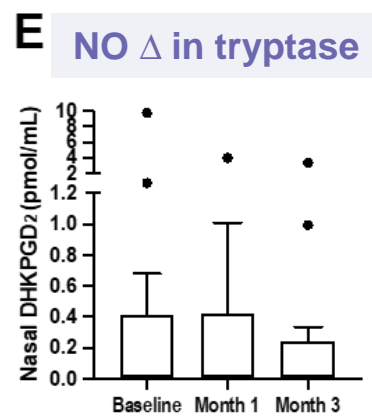
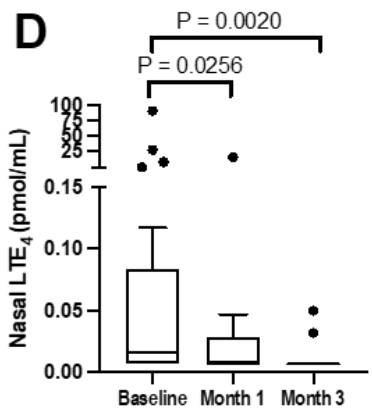
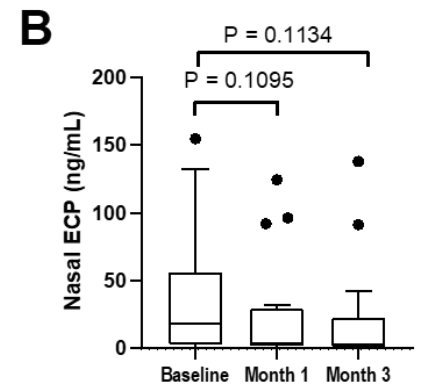
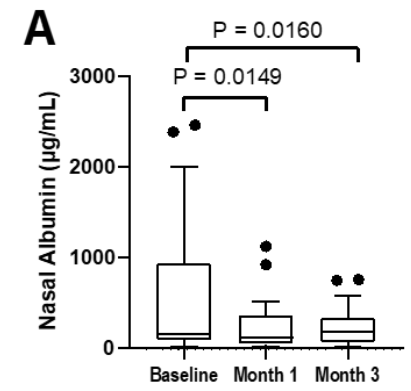
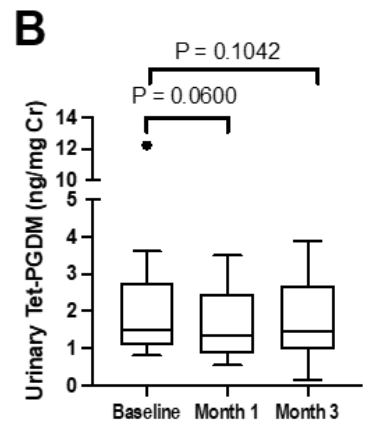
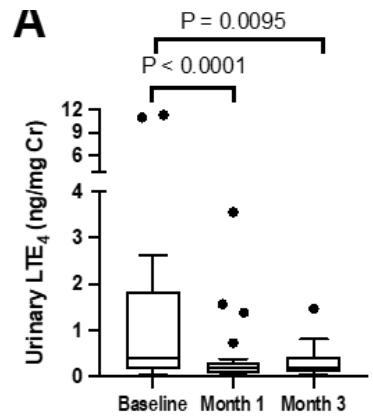
epithelium

↓ Nasal albumin

eosinophil



NO Δ in Nasal ECP

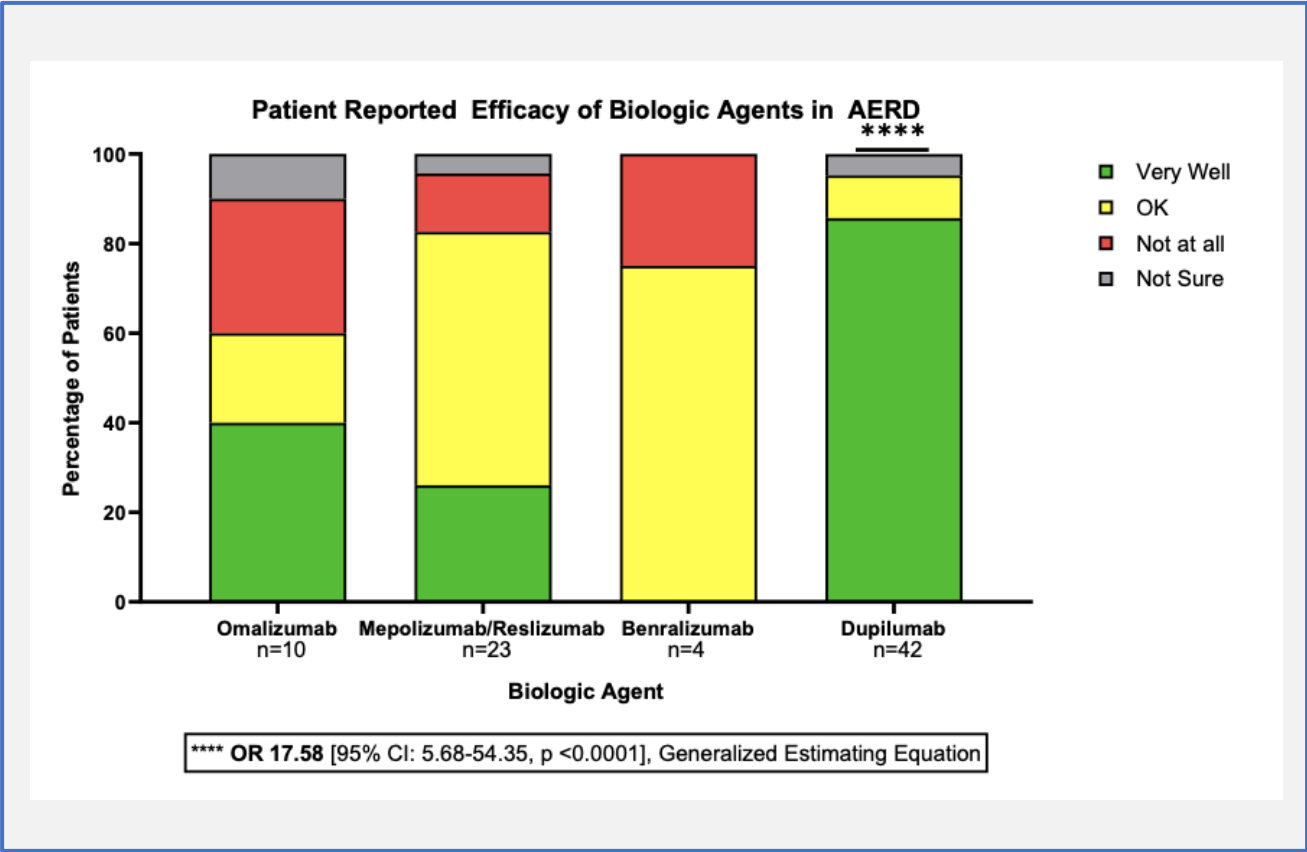
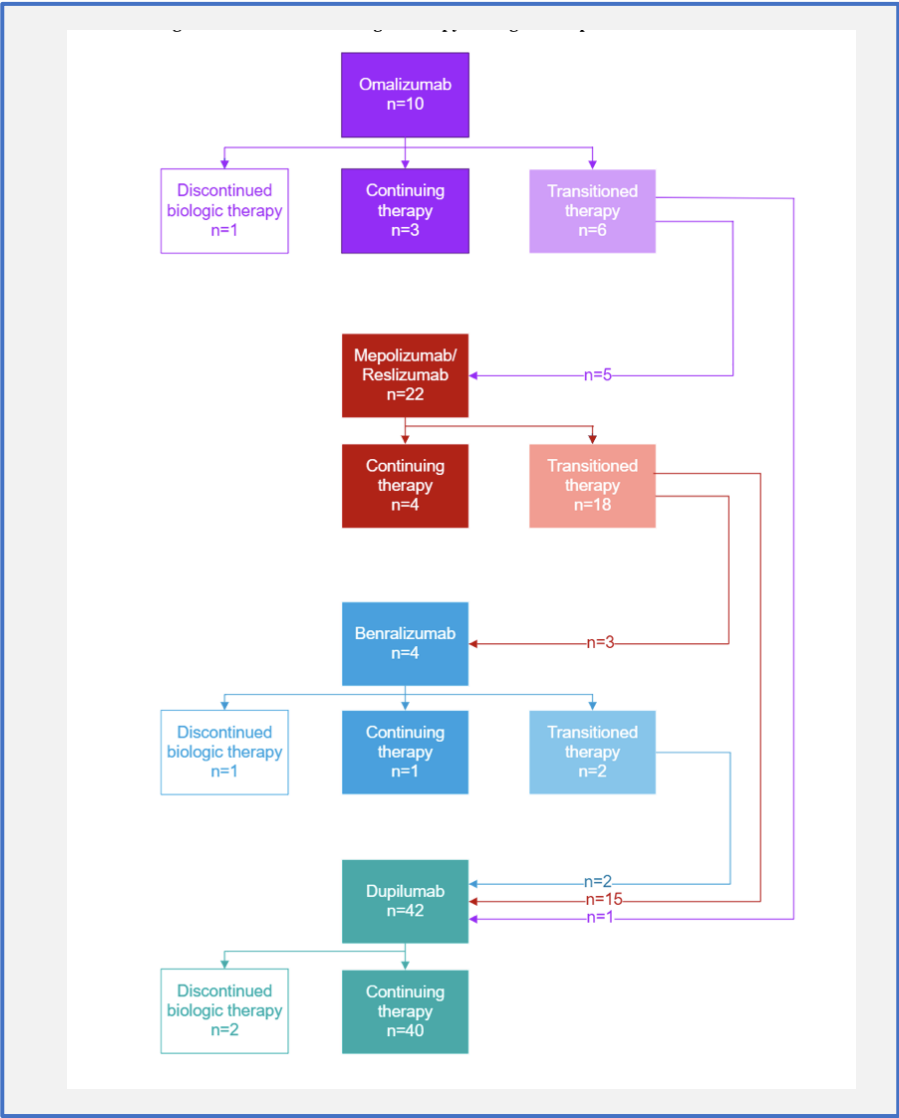


↑ Nasal PGE₂

Time Point	Median	Q1	Q3
Baseline	~1.5	~0.8	~3.0
Month 1	~2.5	~1.5	~10.0
Month 3	~2.0	~1.0	~6.0

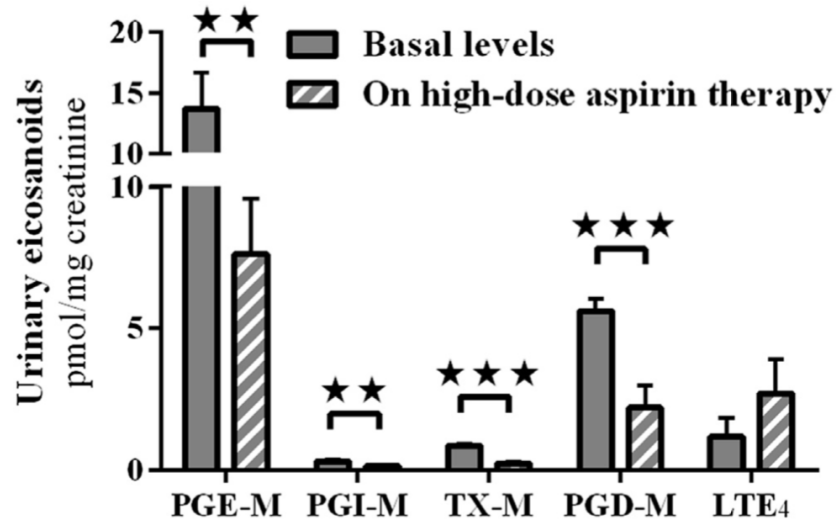
Source of the PGE₂...
 Macrophages?
 Fibroblasts?
 Epithelium?
 Granulocytes?

AERD: Patient reported outcomes – biologic efficacy

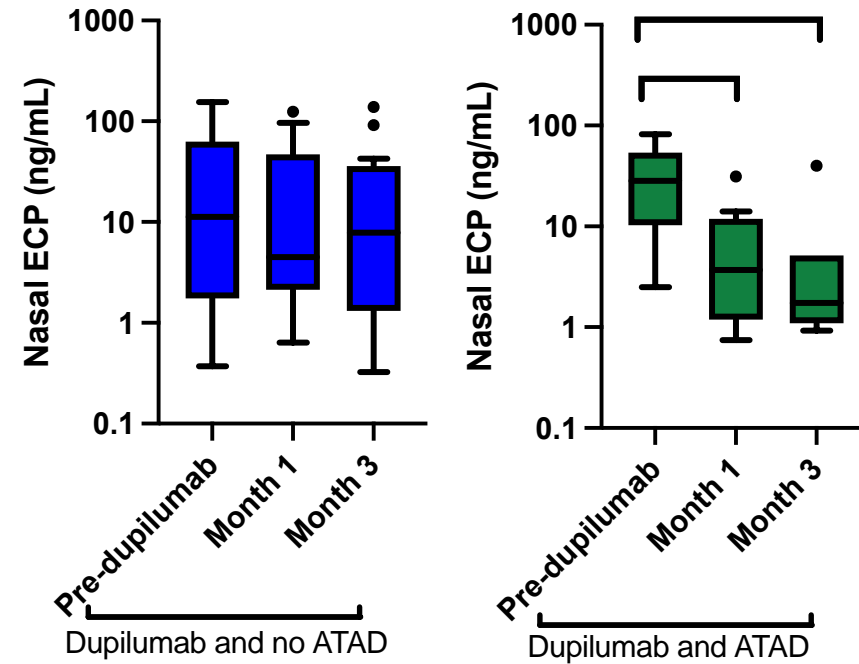


Possible synergy between dupilumab and aspirin therapy

High-dose aspirin therapy lowers urinary PGD-M



Re-analysis of dupilumab prospective study: 8 patients on high-dose asa, 14 patients not on high-dose asa

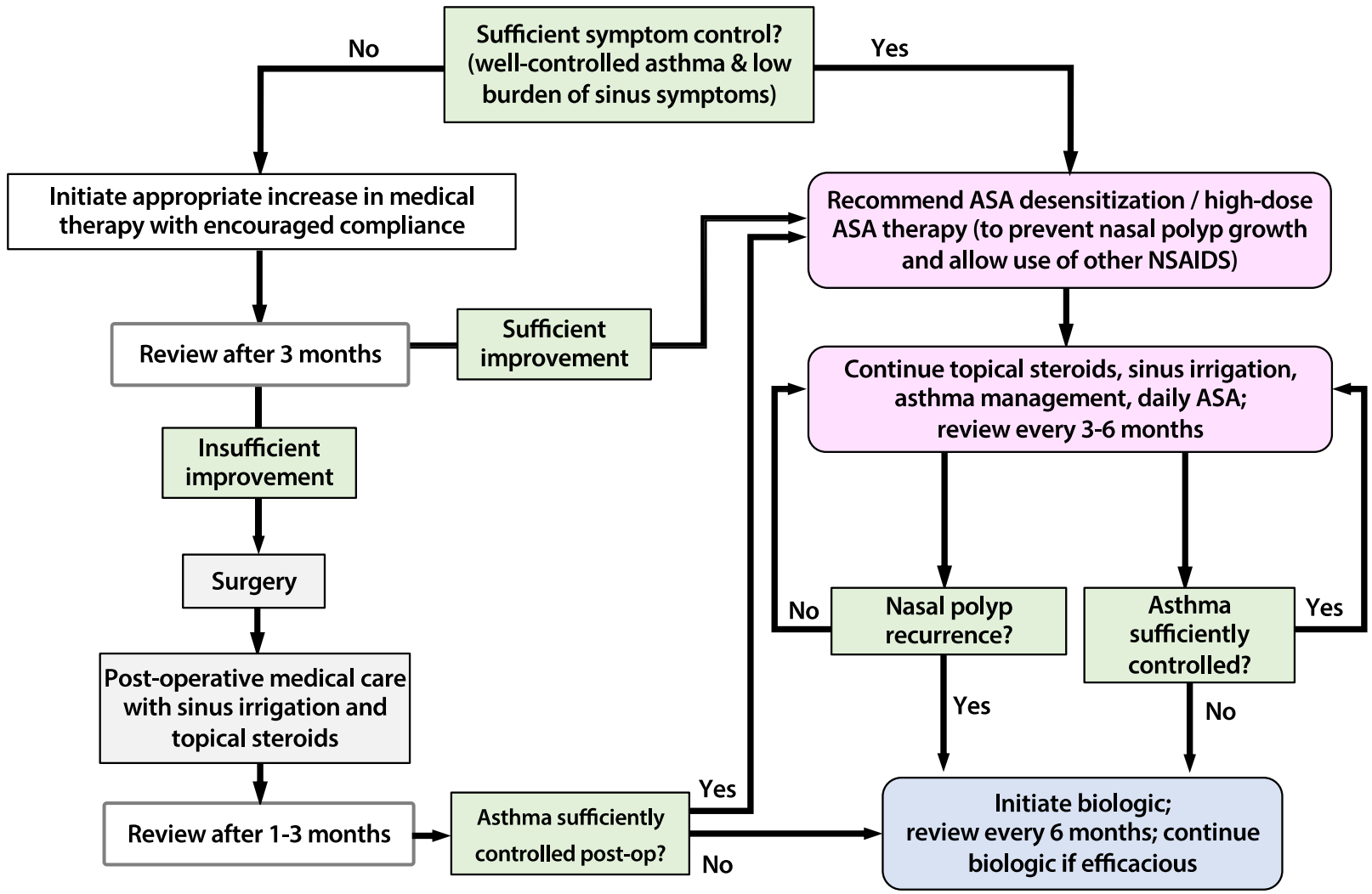


Cahill et al. J Allergy Clin Immunol. 2015 Jan;135(1):245-52.

Buchheit KM et al. Clin Exp Allergy, *In Press*

ATAD: aspirin-therapy after desensitization, ECP: eosinophilic cationic protein, LT: leukotriene, PG: prostaglandin, TX: thromboxane

Where does biologic therapy fit in treatment algorithm for patients with AERD



Questions?

