Managing Asthma with Aspirin-Exacerbated Respiratory Disease

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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, Eli Lilly, Astra Zeneca, Amgen

Overview of slides

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Clinical disease, findings from our BWH AERD Center

Reactions to NSAIDs & aspirin challenge/desensitization

Mechanism and role of leukotrienes & eosinophils

Treatment options – biologics

Treatment options – diet

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

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Asthma

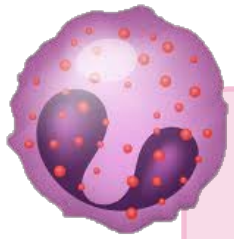
Nasal Polyps (CRSwNP)

Reactions to COX-1 inhibitors

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

We know a lot about what AERD is <u>not</u>

- ❑ Not IgE-mediated allergy to aspirin
- ❑ Not clearly inherited
- ❑ Not childhood disease *(exceptions)*
- ❑ Not due to clear infectious/environmental trigger
- ❑ Not transient

Age and gender: >2500 patients at BWH AERD Center

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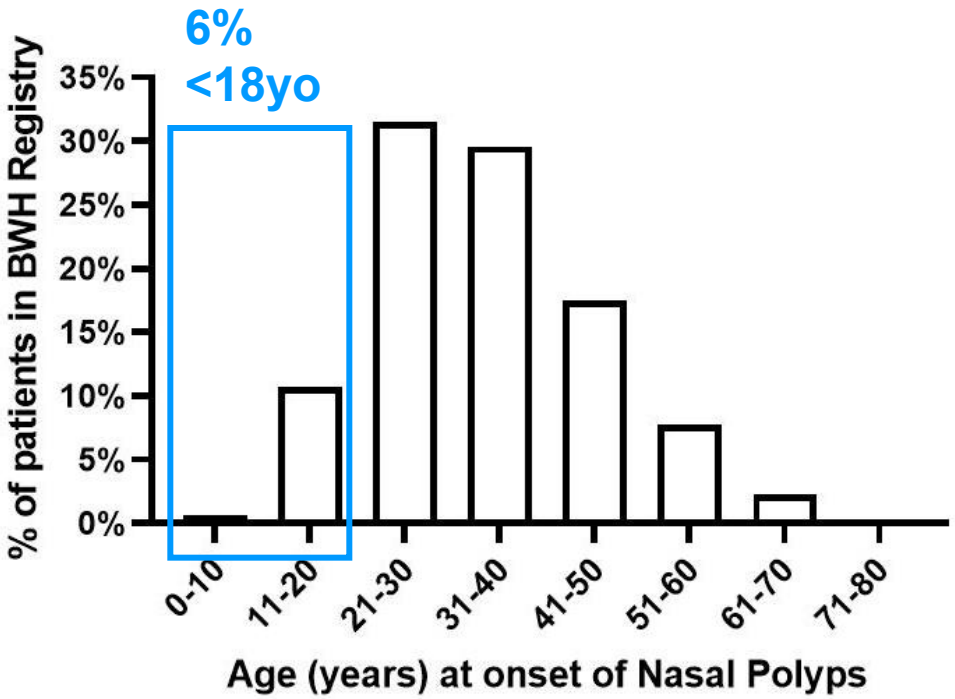
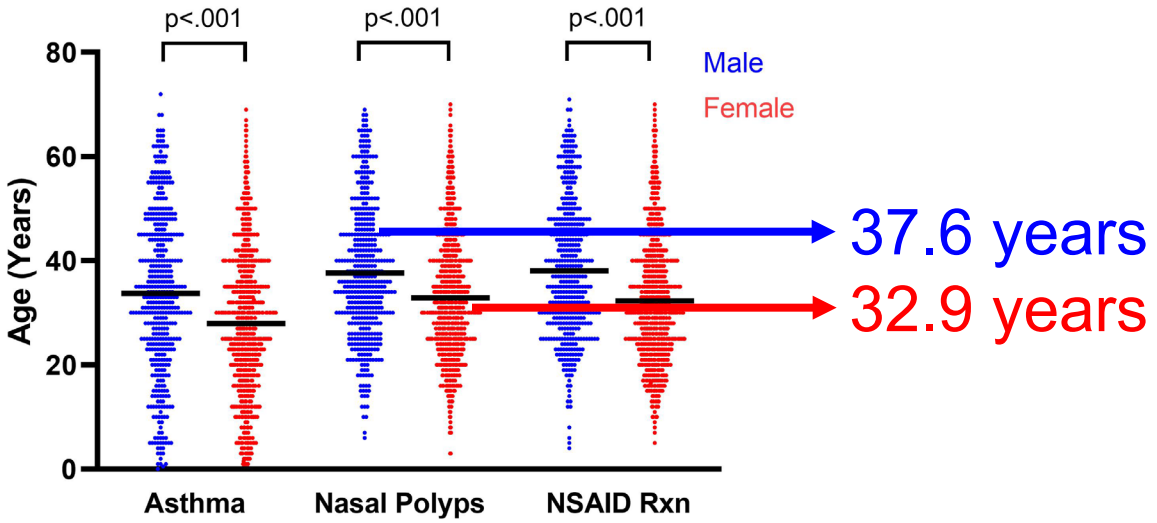
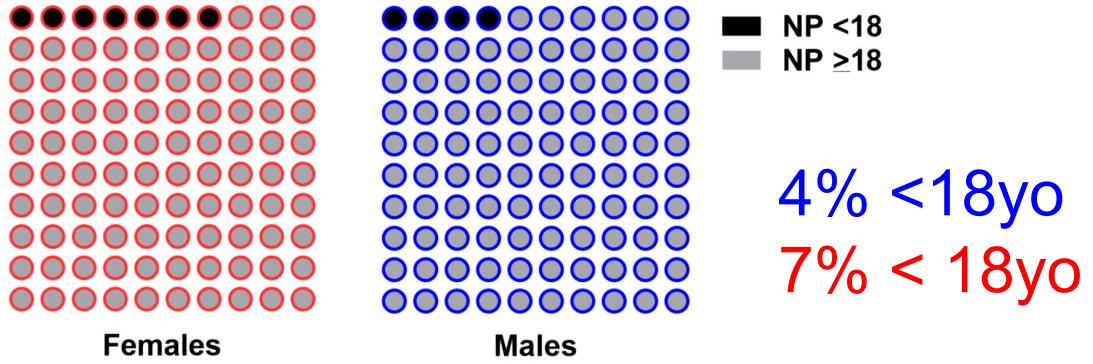
Largely adult-onset disease…







Bensko JC, et al. JACI IP, 2022

Surgery is a key treatment modality for AERD

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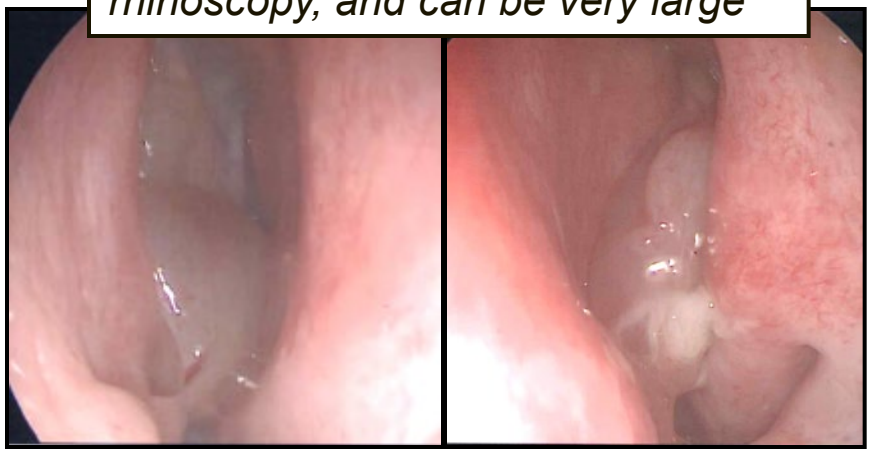
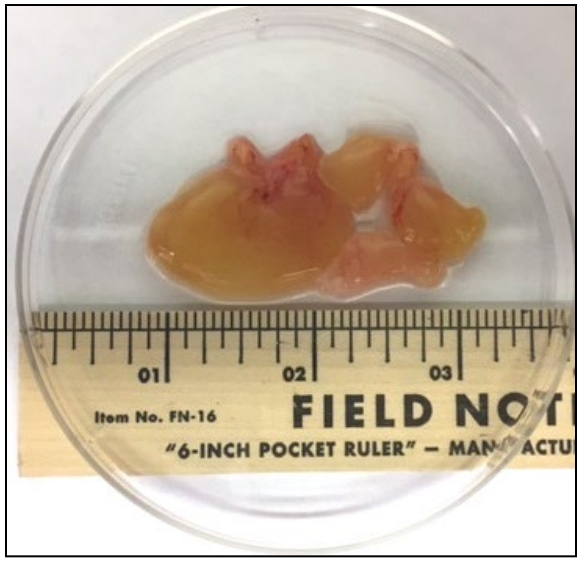
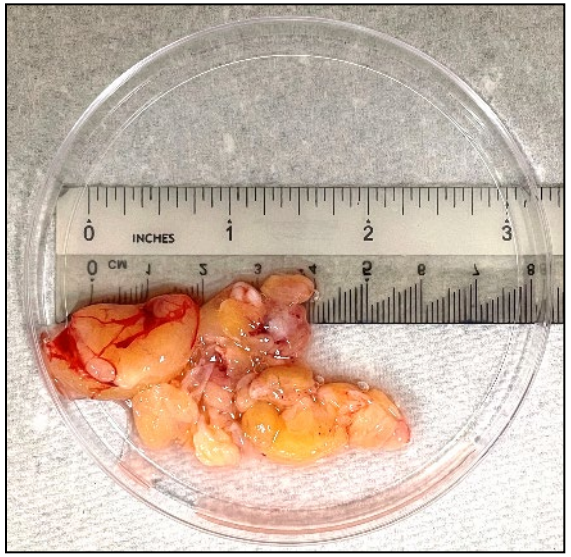
Typical appearance of polyps on rhinoscopy, and can be very large



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

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

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

Challenge

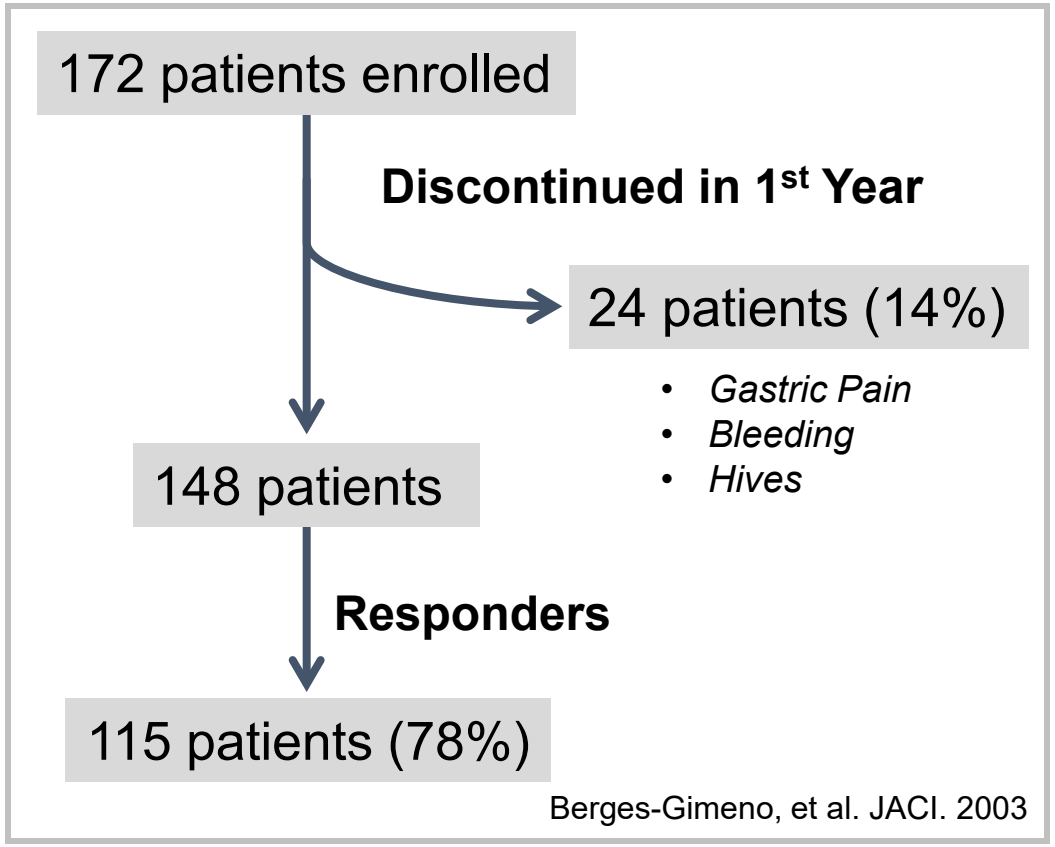
Provocation of symptoms

Desensitization

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

- 67% patients report improvement after 6 months of high-dose aspirin
- ↓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



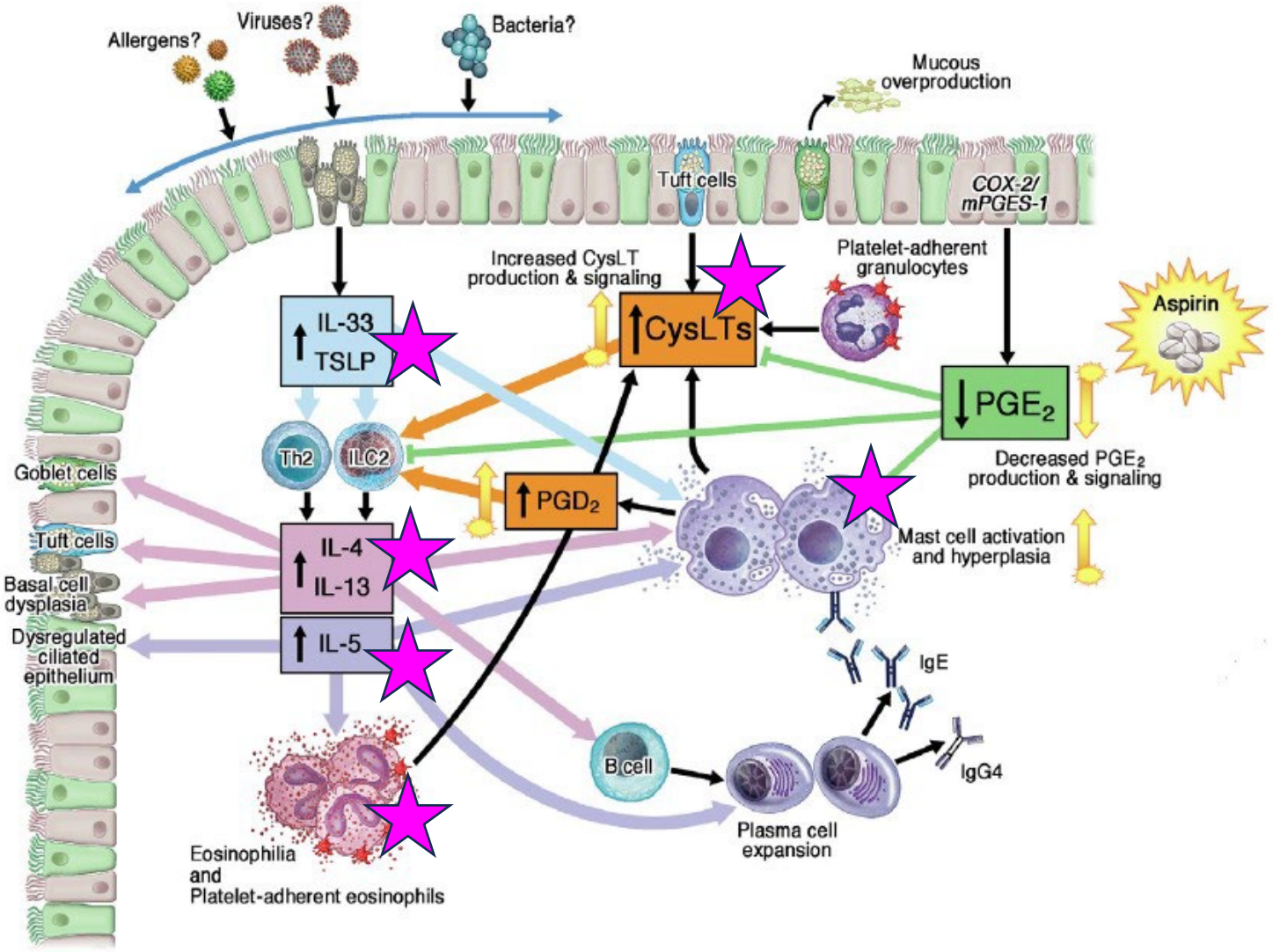
Berges-Gimeno, et al. JACI. 2003

When to do aspirin challenge? → **Preferably before surgery.**

When to desensitize? → **Preferably after surgery.**

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

AERD is a disease of Type 2 Inflammation



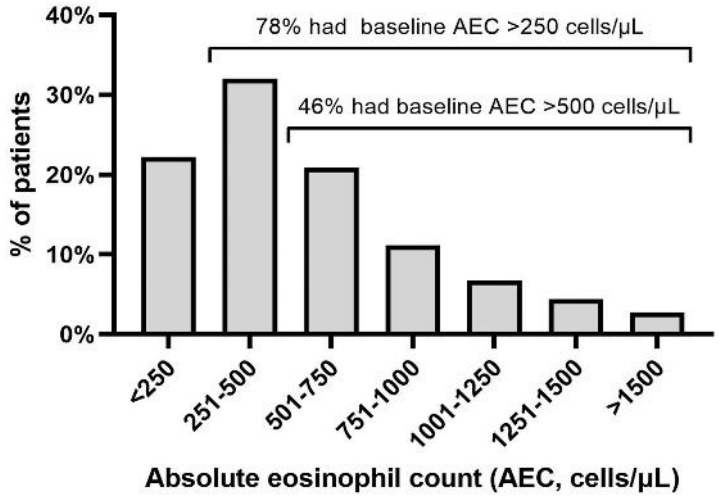
Lots of things are abnormal.

But who can we "blame" for the inflammation in AERD?

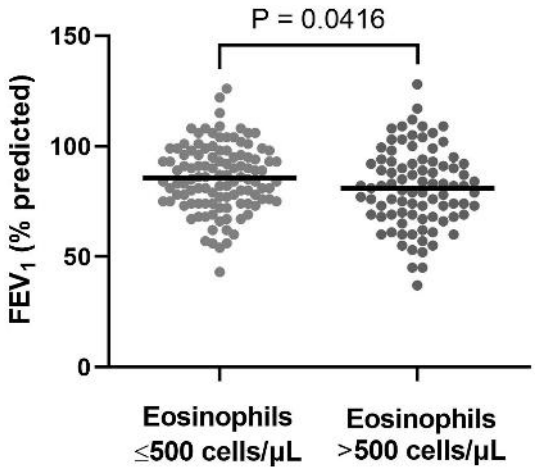
Laidlaw TM, Boyce JA. JACI 2023

What is the role of eosinophils and leukotrienes in AERD?

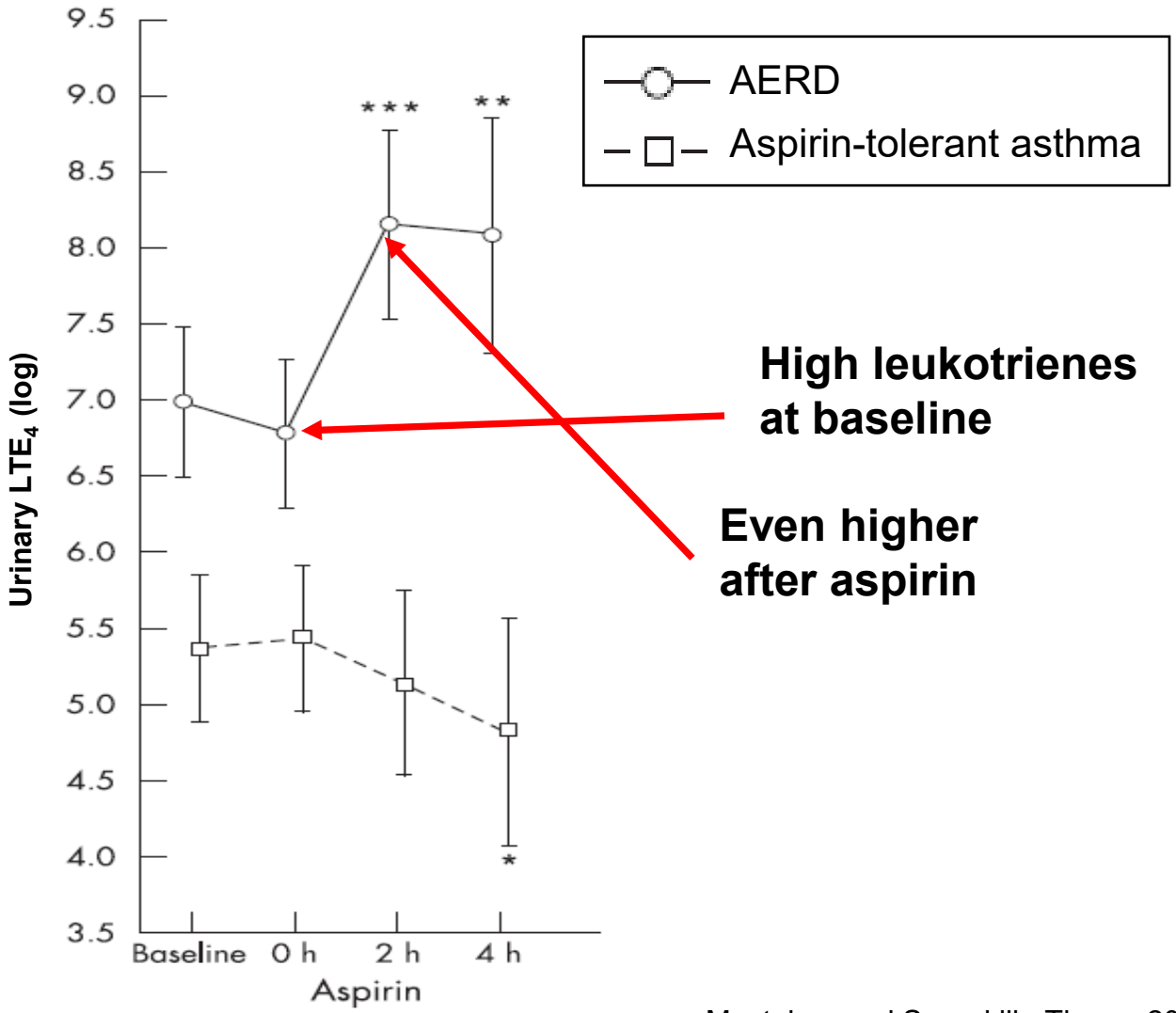
Blood eosinophilia is common



⇧ Blood eos
=
⇩ FEV1



Supron A, et al. JACI IP 2024



Mastalerz and Szczeklik, Thorax 2008

Quantifying upper respiratory disease outcomes in CRSwNP:

"SNOT-22"

Sino-Nasal Outcome Test-22 Questionnaire

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. We would like to know more about these problems and would appreciate you answering the following question to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems, as they have been over the past two weeks. Thank you for your participation.

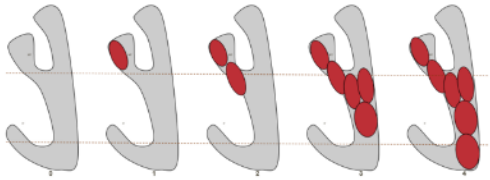
Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how 'bad' it is by circling the number that corresponds with how you feel using this scale →	No problem	Very mild problem	Mild or slight problem	Moderate problem	Severe problem	Problem as bad as it can be
1. Need to blow nose	0	1	2	3	4	5
2. Sneezing	0	1	2	3	4	5
3. Runny Nose	0	1	2	3	4	5
4. Cough	0	1	2	3	4	5
5. Post nasal discharge (dripping at the back of your nose)	0	1	2	3	4	5
6. Thick nasal discharge	0	1	2	3	4	5
7. Ear fullness	0	1	2	3	4	5
8. Dizziness	0	1	2	3	4	5
9. Ear pain/pressure	0	1	2	3	4	5
10. Facial pain/pressure	0	1	2	3	4	5
11. Difficulty falling asleep	0	1	2	3	4	5
12. Waking up at night	0	1	2	3	4	5
13. Lack of a good night's sleep	0	1	2	3	4	5
14. Waking up tired	0	1	2	3	4	5
15. Fatigue during the day	0	1	2	3	4	5
16. Reduced productivity	0	1	2	3	4	5
17. Reduced concentration	0	1	2	3	4	5
18. Frustrated/restless/irritable	0	1	2	3	4	5
19. Sad	0	1	2	3	4	5
20. Embarrassed	0	1	2	3	4	5
21. Sense of taste/smell	0	1	2	3	4	5
22. Blockage/congestion of nose	0	1	2	3	4	5
TOTAL:						

GRAND TOTAL: _____

Score: 0 – 110

Total Polyp Score (TPS)
[Rhinoscopy]

Total Polyp Score



Left ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Right ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

TOTAL _____ (0-8)

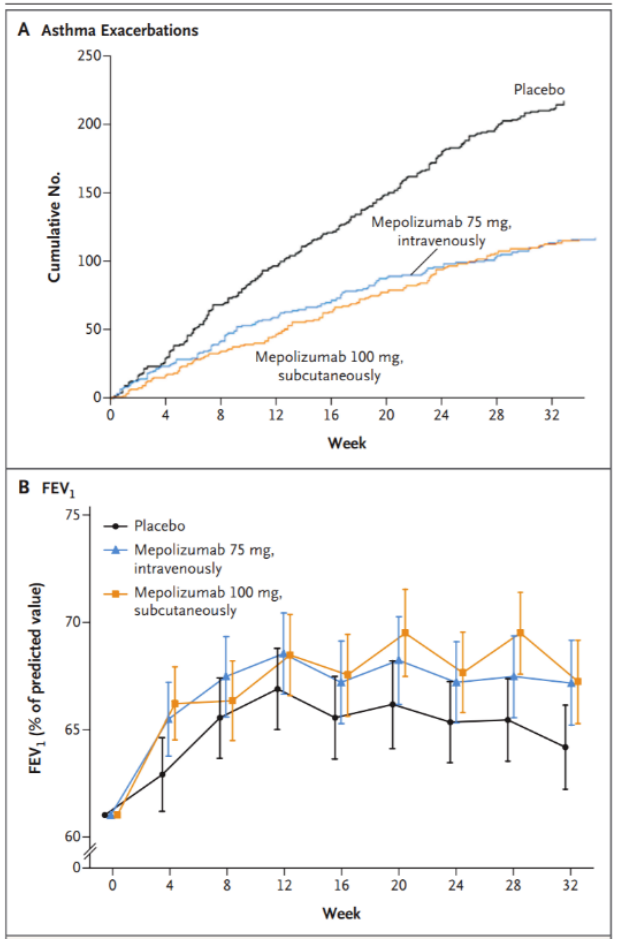
0	No polyps visualized
1	Polyps confined within the middle meatus
2	Polyps extending below the inferior border of the middle turbinate
3	Polyps extending to the inferior border of the inferior turbinate, or polyps
4	Complete nasal obstruction

Score: 0 – 8

"UPSIT"
[Smell Identification Test]

Score: '0' – 40

Eosinophil-inhibiting drugs: Mepolizumab (anti-IL-5) improves asthma control & FEV1 in eosinophilic asthma



↓ 50% asthma exacerbations

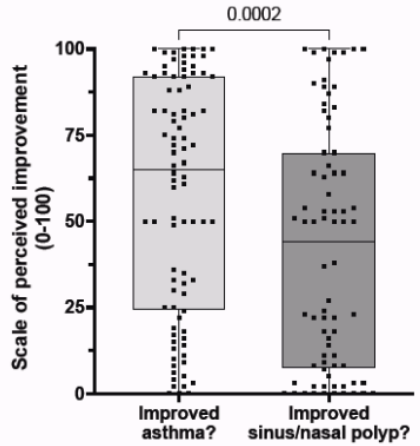
↓ 70% if AEC ≥500

↑ 100mL in FEV1

↑ 130-185mL if AEC ≥500

Ortega HG, et al. NEJM 2014

But… improves perceived asthma control more than sinus/nasal polyp control



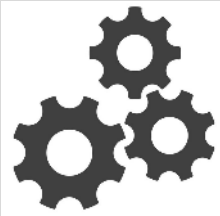
Sohail, et al. Allergy 2024

SYNAPSE; Phase 3 nasal polyps

- 407 patients total
  - **↓ TPS of 0.73 at 52 wks**
    - >20% worsened TPS; >25% no TPS change
  - No improvement in UPSIT
- 108 AERD patients
  - **↓ TPS of 0.89 at 52 wks**

Han JK, et al. Lancet Resp Med 2021

Leukotriene-modifying drugs: Zileuton is more effective in AERD than in aspirin-tolerant asthma

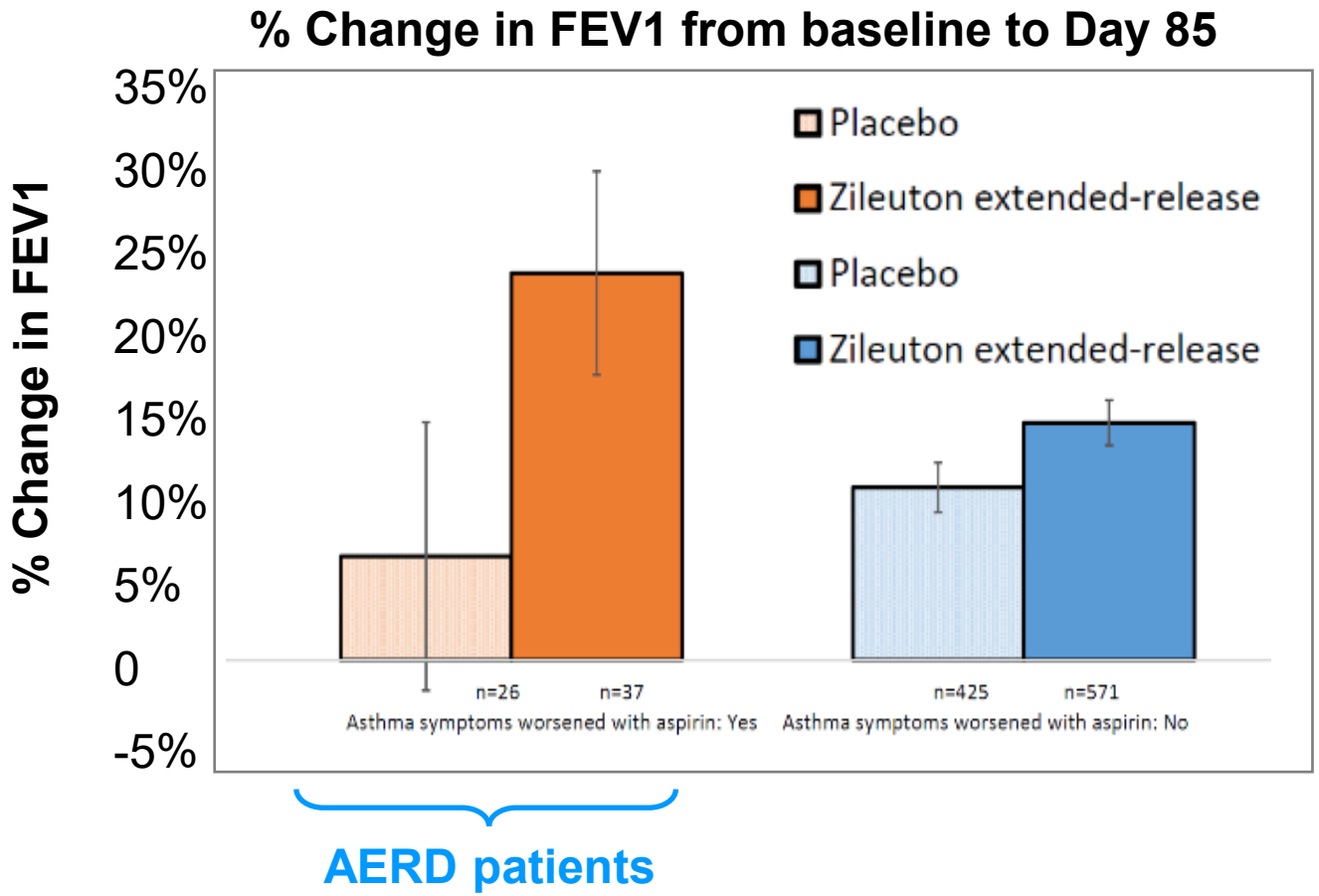


Zileuton (5-lipoxygenase inhibitor FDA approved for asthma in 1996):

- Increases provocative aspirin dose
- Can completely block NSAID reactions
- Useful for severe symptoms during aspirin reaction

E Israel, et al. AmRevRespirDis, 1993

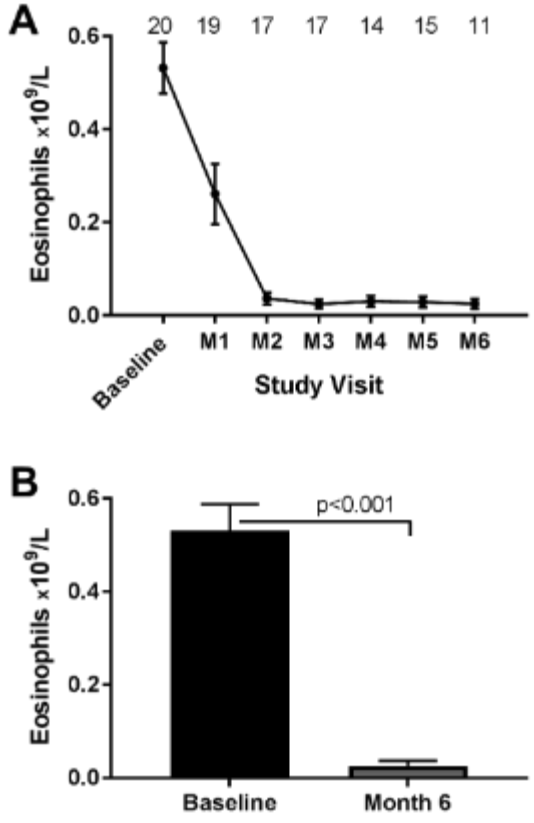
"Efficacy of Zileuton: Analysis from Two Phase 3 Studies"



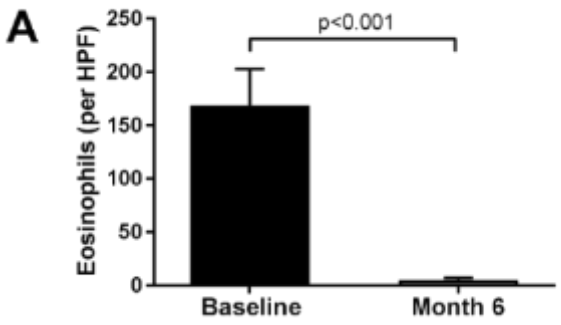
AAAAI 2017 Poster L30

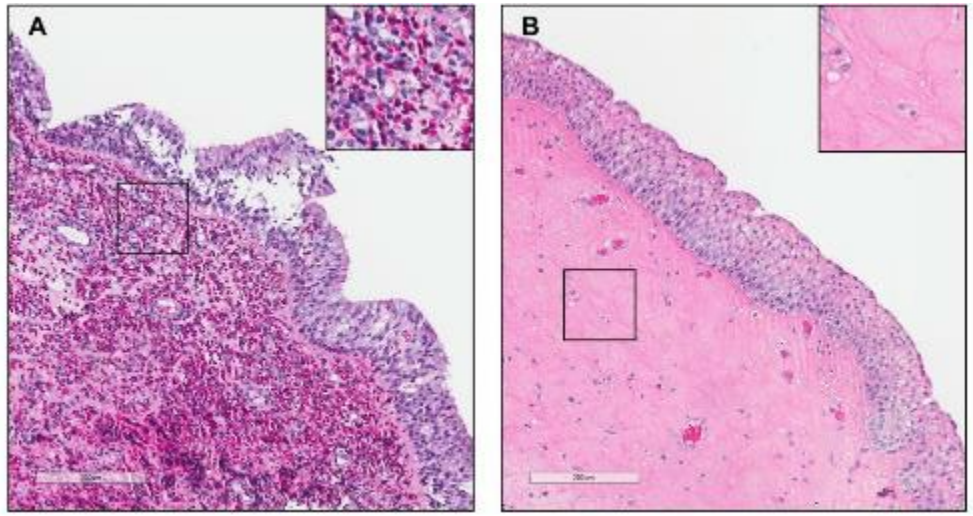
Dexpramipexole in CRSwNP – how important are eosinophils?

Blood eosinophils decrease

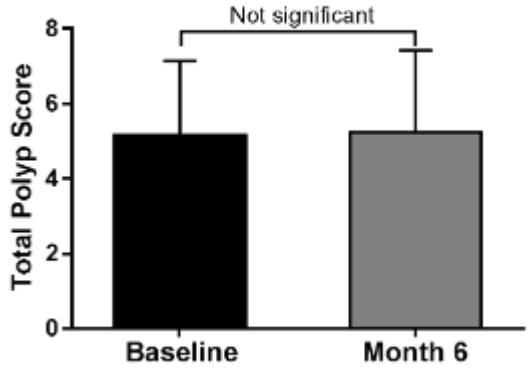


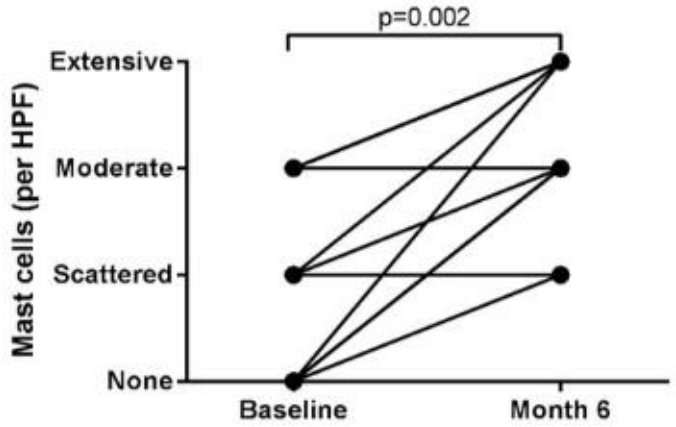
Polyp eosinophils decrease





No improvement in polyp size





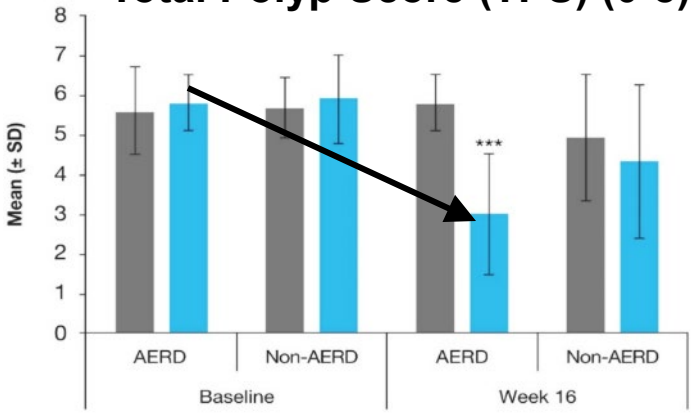
Laidlaw TM, et al. Laryngoscope. Feb 2019

Dupilumab (anti-IL4Rα) in AERD

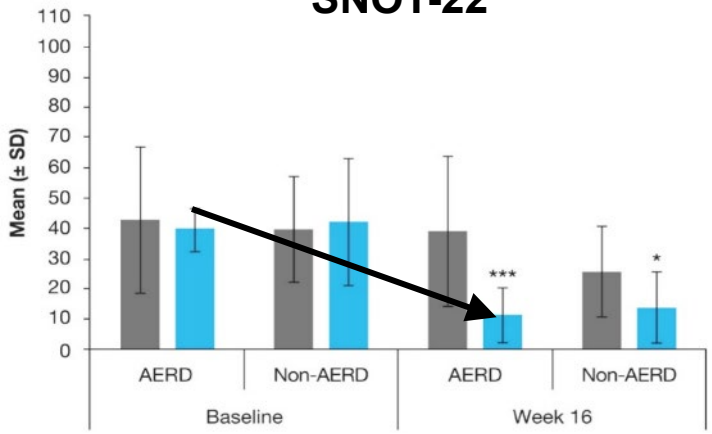
Re-analysis of Phase 2 study;
19/60 patients had aspirin sensitivity

Dupilumab Placebo

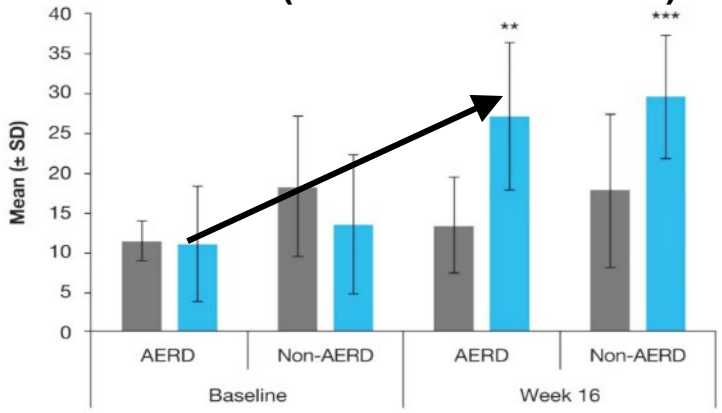
Total Polyp Score (TPS) (0-8)



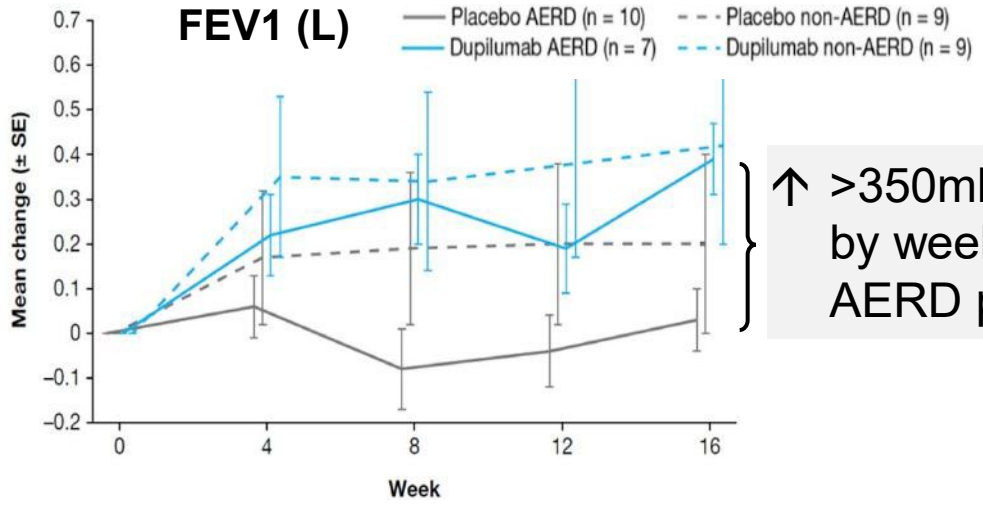
SNOT-22



UPSIT (# scents identified)



FEV1 (L)



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

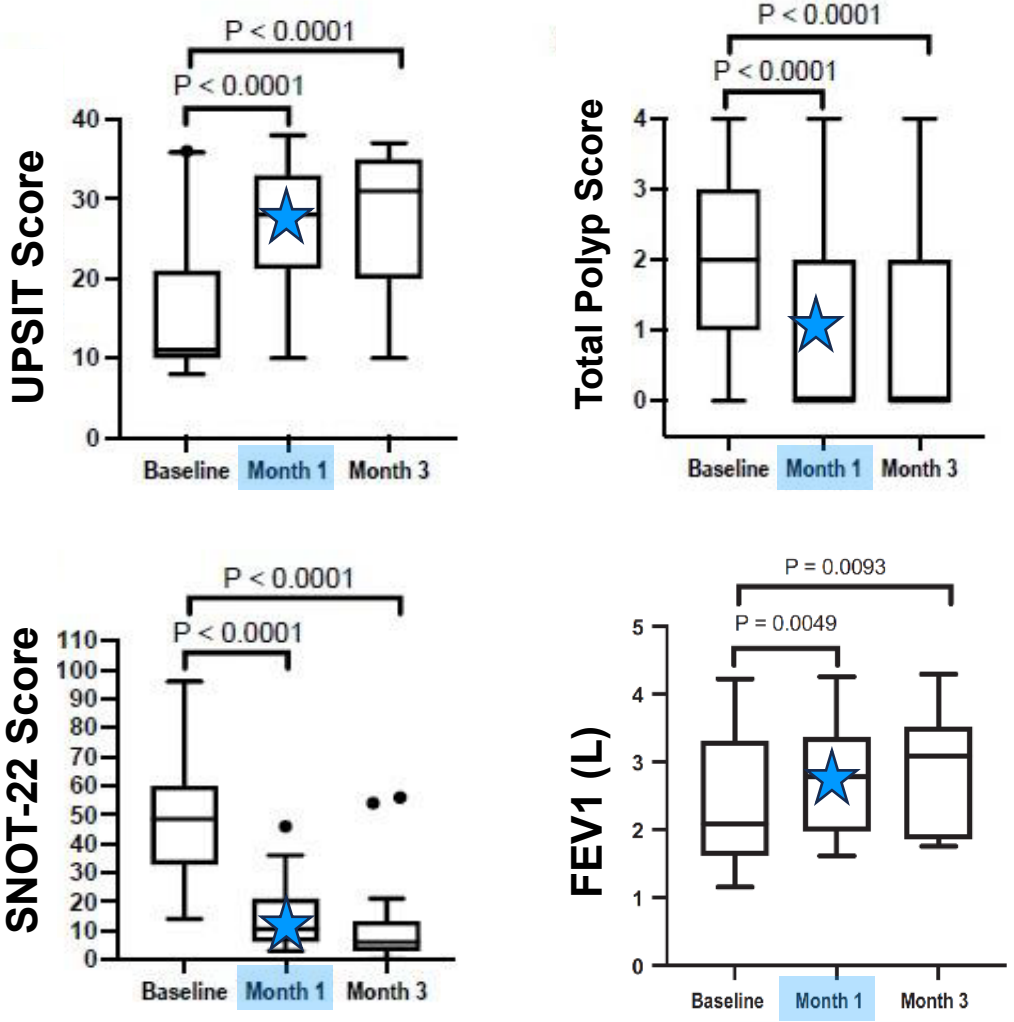
Laidlaw TM, et al. JACI In Pract. 2019.

SINUS-52; Phase 3 nasal polyps

- 448 patients total
  - ↓ TPS of 2.1 at 24 wks
  - Smell (UPSIT) improved by 11 scents
- 79 AERD patients
  - ↓ TPS of 2.5 at 24 wks

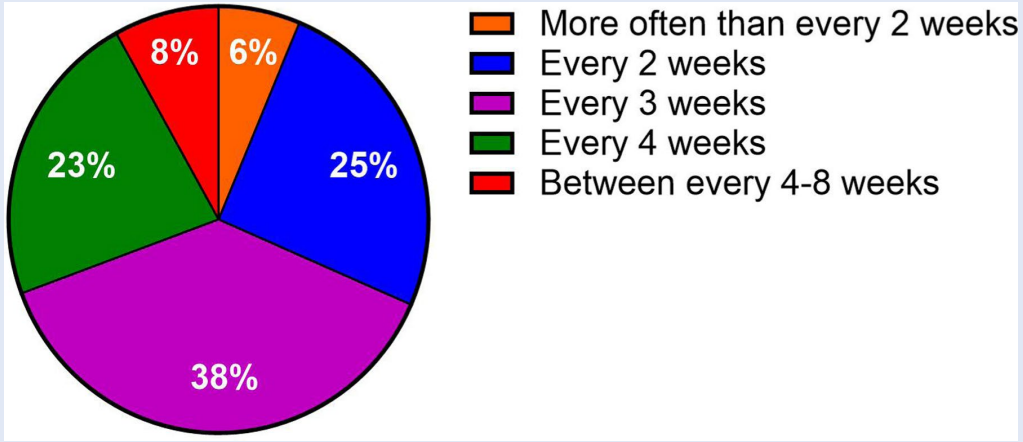
Bachert C, et al. Lancet 2019

Anti-IL4Rα (dupilumab) rapidly improves upper & lower respiratory symptoms in AERD



Buchheit K, et al. JACI 2022

Many AERD patients can extend dosing interval of dupilumab



Brown AN, et al. JACI IP 2024

Efficacy of anti-TSLP with tezepelumab in AERD

(43 patients in NAVIGATOR had AERD)

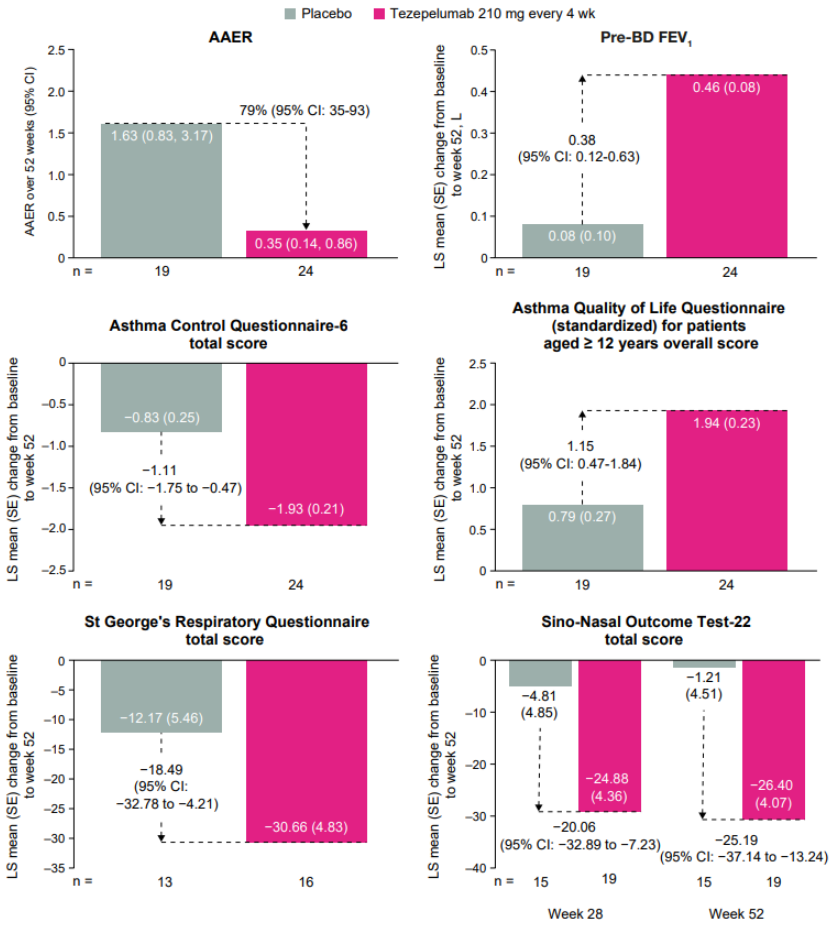


FIGURE 1. Annualized asthma exacerbation rate (AAER) over 52 weeks and changes from baseline to week 52 in lung function and patient-reported outcomes in patients with coexisting aspirin-exacerbated respiratory disease. *BD*, bronchodilator; *LS*, least-squares; *Q4W*, every 4 weeks.

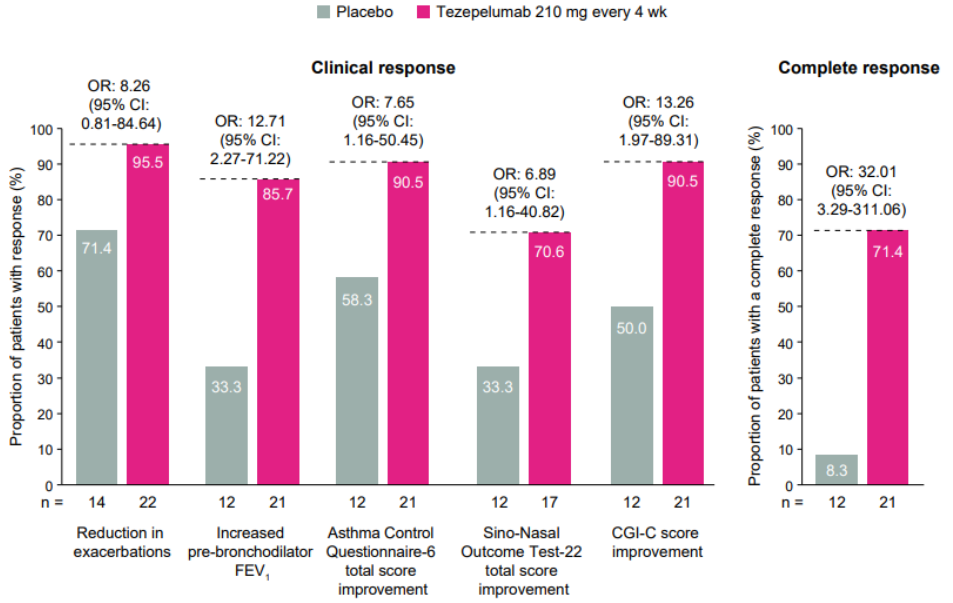


FIGURE 2. Proportion of patients with coexisting aspirin-exacerbated respiratory disease who had a clinical response and a complete response at week 52. Complete response was defined as a clinical response for all four asthma-related criteria. *CGI-C*, Clinical Global Impression of Change; *OR*, odds ratio; *Q4W*, every 4 weeks.

	AERD	NSAID-tolerant
AAER	79% reduction	56% reduction
Pre-BD FEV1	0.38 L	0.12 L
ACQ-6	-1.11	-0.30
“Complete responders”	71.4%	46.9%

Laidlaw TM, et al. JACI In Practice 2025

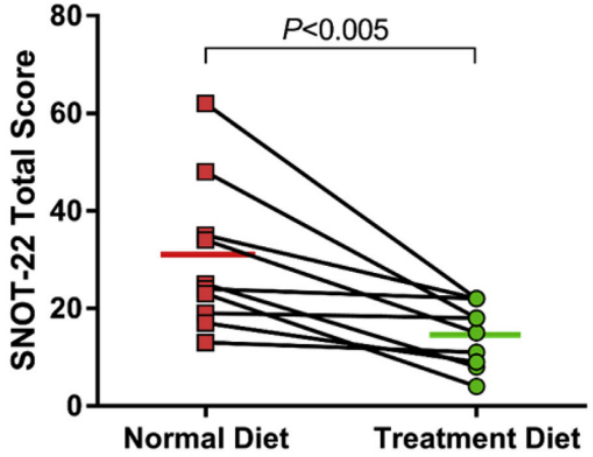
Diet to reduce omega-6 fatty acids (and increase omega-3) can decrease leukotrienes and improve symptoms in AERD

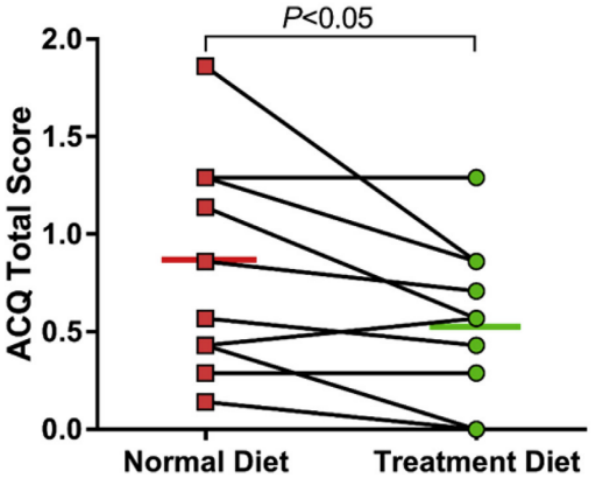
Good:

- 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:

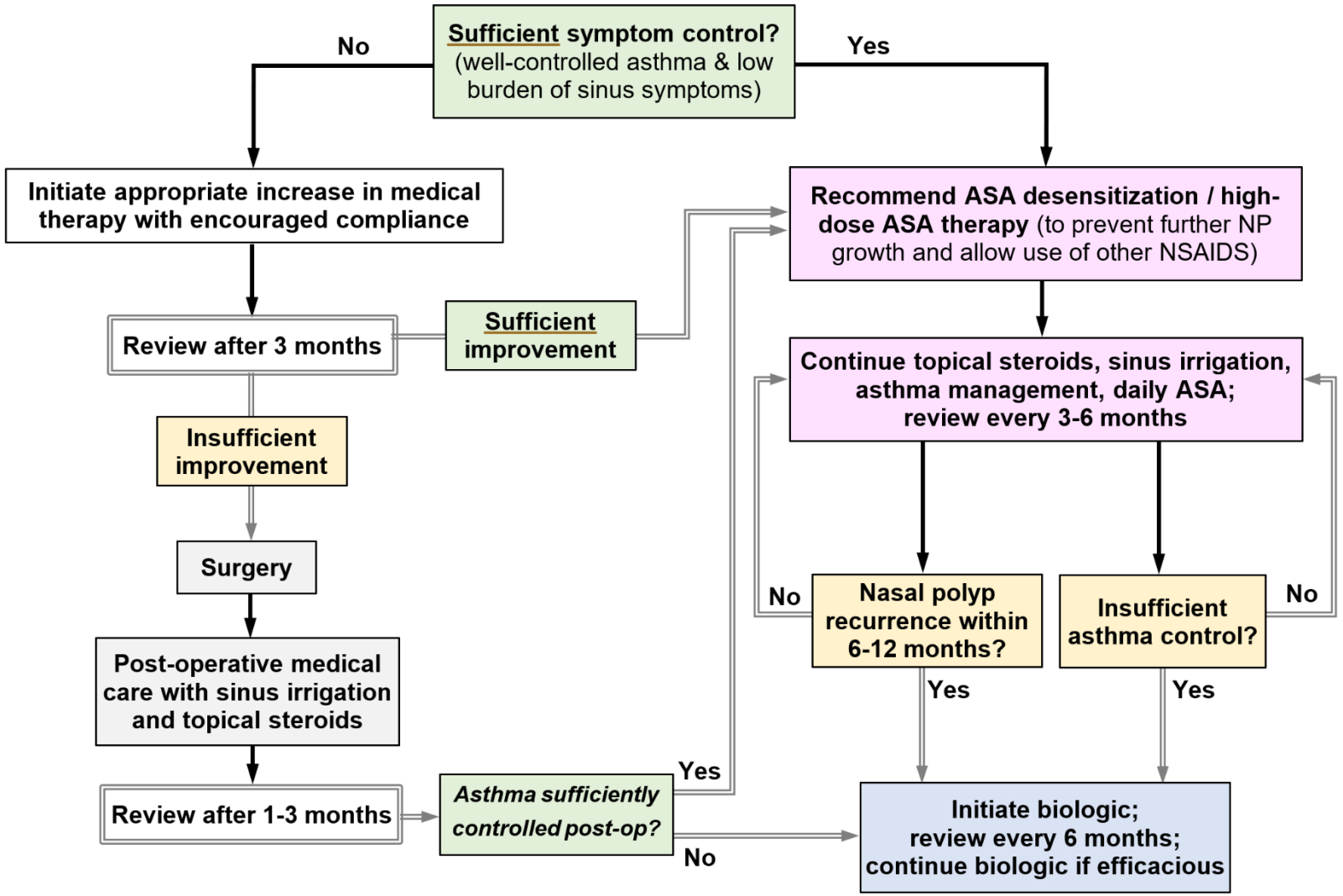
- Vegetable oils (corn, soybean, safflower)
- Margarine
- Meats if animals ate corn/soy
- Eggs/dairy if animals ate corn/soy





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

Where biologics fit into 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?**
Mediators	• **CysLTs** contribute to low FEV_1 & aspirin reactions	• **IL-4/IL-13** and **TSLP** drive substantial pathology • Role of **IL-5?**

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