

# Aspirin Exacerbated Respiratory Disease: Diagnosis and Management



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# PSB Disclosures

➤ None

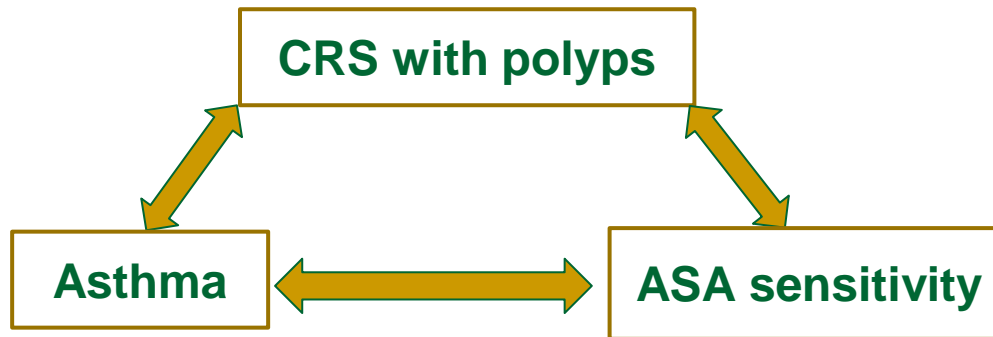
# AERD (Samter or Aspirin Triad): History



[www.waojournal.org](http://www.waojournal.org)

- “Angioedema and rhinitis, nasal polyposis, and bronchial asthma of aspirin-sensitive patients are acquired diseases that develop, as a rule, after middle age in predominantly non-atopic patients....The substances that have been found to induce aspirin-like symptoms have one characteristic in common—they are strong minor analgesics and include pyrazolones and indomethacin as well as aspirin.”

# AERD: Definition



- Upper and lower respiratory tract reactions after ingestion of ASA and NSAIDS
- Best described as pseudo-allergy (not IgE mediated)
- Reactions triggered by wide range of structurally distinct medications that inhibit COX-1
- Can cross-react with Tylenol (>1000mg)

**Table 1. Cyclooxygenase 1 (COX-1) and Cyclooxygenase 2 (COX-2) Inhibitors That Trigger Respiratory Reactions in Patients with Aspirin-Exacerbated Respiratory Disease (AERD).\***

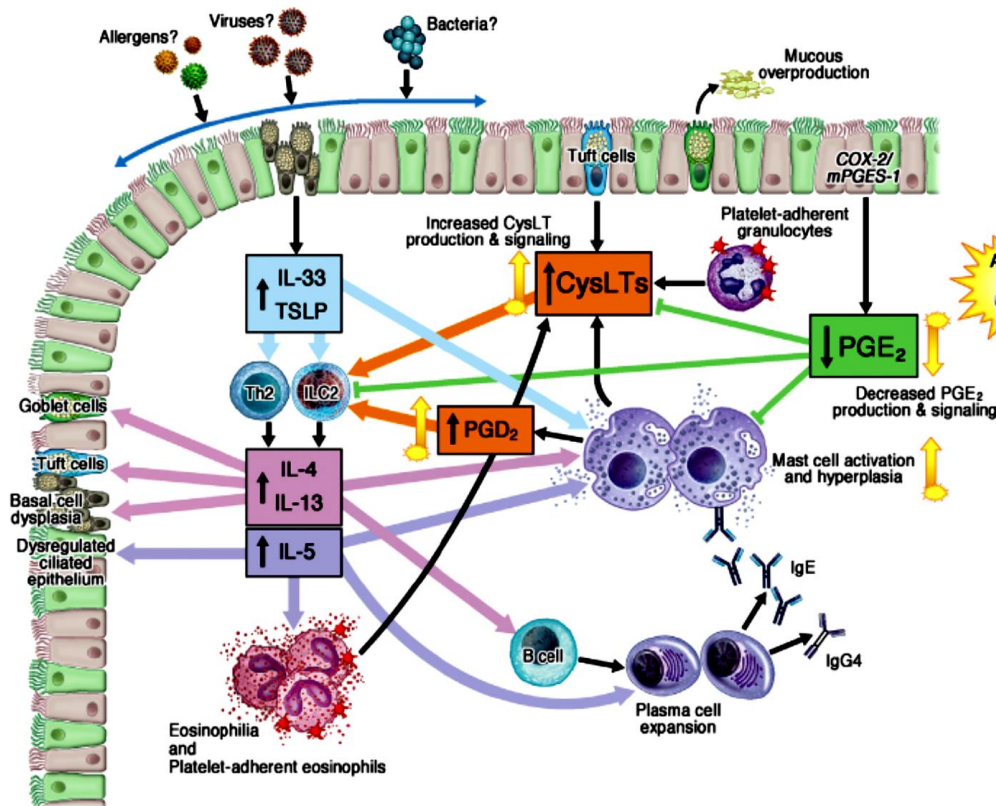
Medication	Route of Administration
<b>Highly selective COX-1 inhibitors</b>	
Acetylsalicylic acid	Oral (OTC)
Antipyrine–benzocaine	Otic only (OTC)
Benoxaprofen	Oral
Diclofenac	Oral, topical
Etodolac	Oral
Fenoprofen	Oral
Flurbiprofen	Oral
Ibuprofen	Oral (OTC)
Indomethacin	Oral
Ketoprofen	Oral, topical
Ketorolac	Oral, IM, IV, nasal
Meclofenamate	Oral
Dipyron	Oral
Mefenamic acid	Oral
Naproxen	Oral (OTC)
Oxaprozin	Oral
Piroxicam	Oral
Tolmetin	Oral
<b>Weakly selective COX-1 inhibitors</b>	
Acetaminophen	Oral (OTC)
Choline magnesium trisalicylate	Oral
Diflunisal	Oral
Salsalate	Oral
<b>Highly selective COX-2 inhibitors</b>	
Celecoxib	Oral
Etoricoxib†	Oral
Lumiracoxib†	Oral
Parecoxib†	IV, IM
<b>Preferentially selective COX-2 inhibitors (COX-1 inhibition at high doses)</b>	
Meloxicam	Oral
Nabumetone†	Oral
Nimesulide†	Oral, topical

# Prevalence of AERD

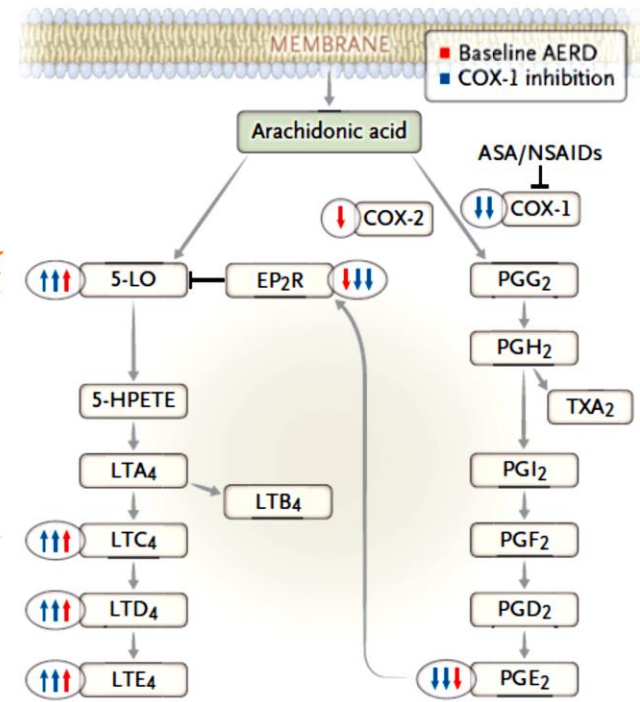
Patient Group	Prevalence
Asthma	7.3%
Severe asthma	14.9%
Nasal polyps	9.7%
Chronic rhinosinusitis	8.7%

- Based on systematic analysis of 27 studies
- May affect 20-40% of asthmatic patients with CRS with polyposis

# Pathophysiology



White AA, Stevenson DD. *NEJM* 2018.



**Confluence of Genetic Factors and Environmental Insults**

# Natural History

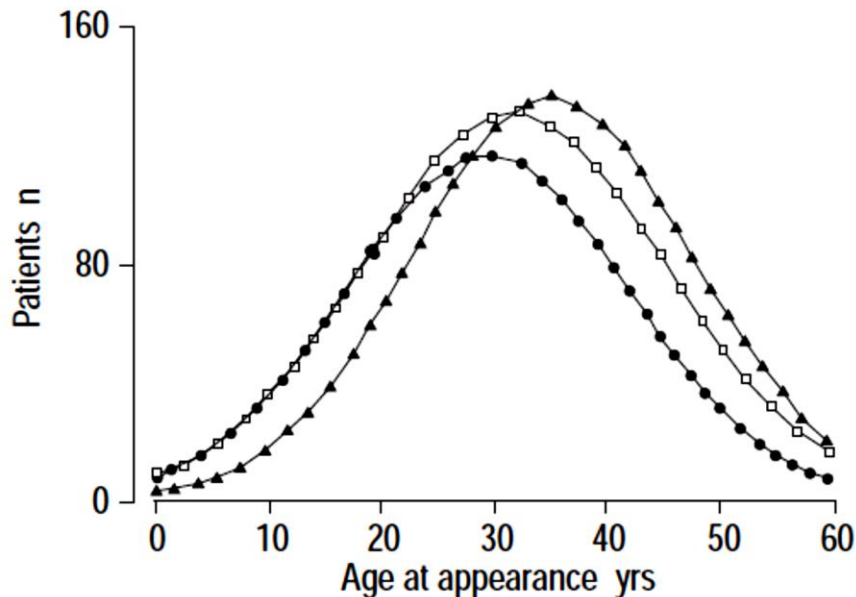


Fig. 1. – Distributions of appearance of the first symptoms of rhinitis (●), asthma (□) and aspirin intolerance (▲).

- 500 patients at 16 centers
- Characteristic pattern....
- Persistent rhinitis appeared at mean age of 30 years
- Asthma lagged mean 2 years
- ASA intolerance and nasal polyps presented 4 years later

# Clinical Presentation

- Acute reactions typically begin in 30 min to 3 hours
- Dose related symptoms
- **Upper airway**: nasal congestion, watery rhinorrhea, periorbital edema, and/or injection of the conjunctiva
- **Lower airway**: wheezing, dyspnea, cough, and chest tightness (marked fall in FEV<sub>1</sub>)
- Less commonly GI symptoms (abdominal pain, nausea)
- Urticaria and/or angioedema occurs in ~15%



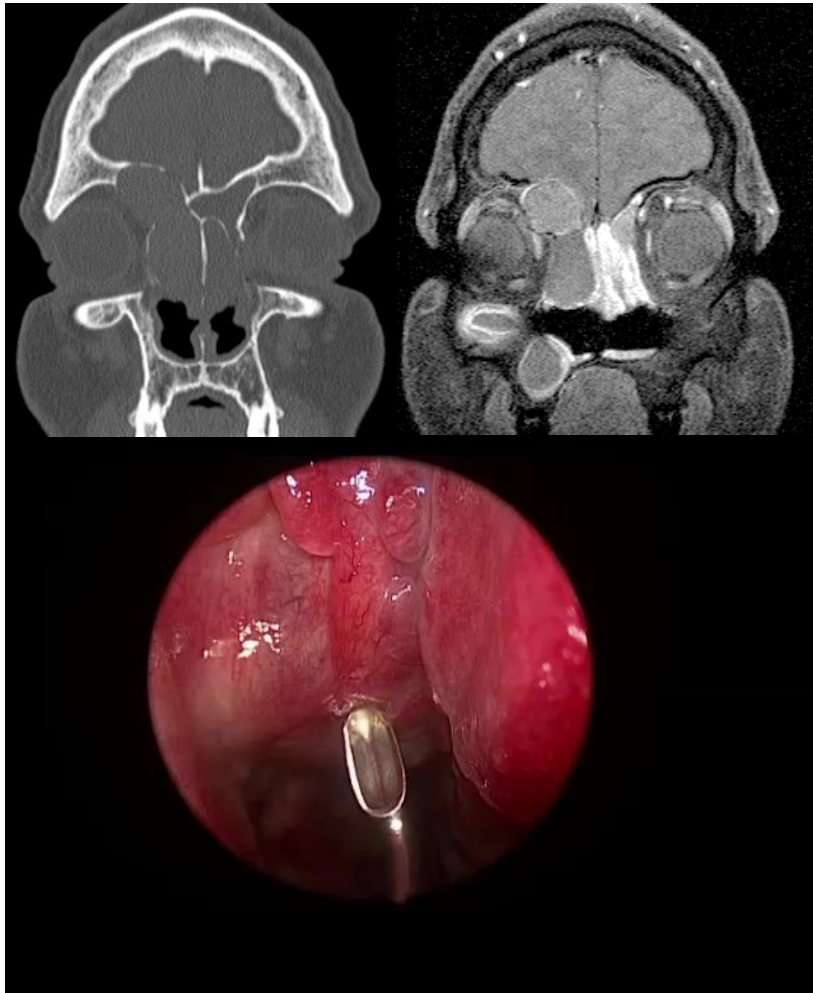


# Not All AERD is the Same....

Class	%	Phenotype
1	18.9%	Moderate asthma, intense upper airway symptoms, blood eosinophilia
2	34.8%	Mild asthma, relatively well controlled, low health care use
3	41.3%	Severe, poorly controlled asthma, severe exacerbations and airway obstruction
4	5%	Poorly controlled asthma with frequent and severe exacerbations in female subjects

- *Atopic status did not affect class membership*
- Patients with intense upper airway symptoms had highest levels of blood eosinophilia and urinary LTE4

# Clinical Profile of AERD



- Average age: 34 years
- 57% females
- Type I hypersensitivity: 66%
- Abnormal sinus CT: 99%
- Oral steroids: 77%
- Sinusitis episodes: 5.5/year
- Previous ASA/NSAID reactions:
  - One: 27%
  - Two: 33%
  - Three: 36%

# Clinical Profile: AERD Portends More Severe Disease....

Comparison Between Patients With and Without ASA Sensitivity

Objective Parameters	ASA Sensitivity, n = 36, Mean ( $\pm$ SD)	No ASA Sensitivity, n = 189, Mean ( $\pm$ SD)	P Value
Endoscopy score	11.7 ( $\pm$ 2.9)	8.5 ( $\pm$ 4.0)	<.0001
CT score	17.1 ( $\pm$ 4.4)	10.3 ( $\pm$ 5.4)	<.0001
Absolute eosinophil count	0.6 ( $\pm$ 0.4)	0.4 ( $\pm$ 0.3)	.003
Total IgE	191.7 ( $\pm$ 294.1)	150.9 ( $\pm$ 235.9)	.186*

1. AERD patients are more likely to undergo complete vs. targeted surgery<sup>2</sup>
2. AERD patients are significantly more likely to have recurrence and undergo second surgery (OR = 2.7;  $p < 0.01$ ) than patients w/wo asthma<sup>3</sup>

<sup>1</sup>Batra PS, et al. *Laryngoscope* 2013;123:E1–E11.

<sup>2</sup>DeConde AS, et al. *Int Forum Allergy Rhinol* 2015;5:691–700.

<sup>3</sup>Jang DW, et al. *Laryngoscope* 2014;124:34-7.

# Diagnostic Considerations:

History of ASA/NSAID reactions often guide diagnosis...

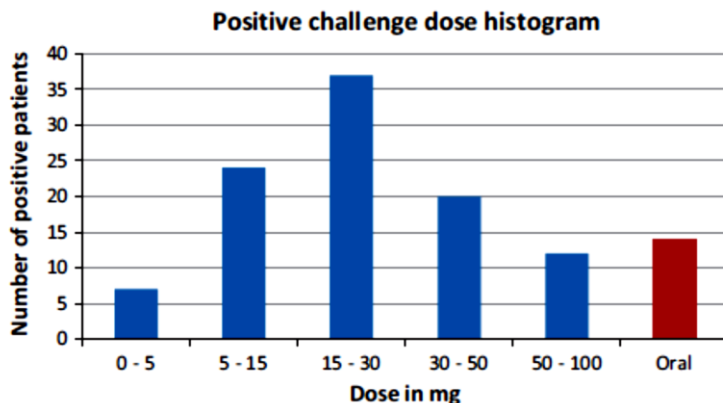
**Table 2. Likelihood of AERD on the Basis of Historical Information.\***

Historical Information	Likelihood of Positive OAC†
<b>In patients with asthma and opacified sinuses on imaging</b>	
Respiratory symptoms within 90 min after ingestion of an NSAID on one occasion	80%
Respiratory symptoms within 90 min after ingestion of 1 or 2 NSAIDs on $\geq 2$ occasions	89%
Mild respiratory symptoms (treated by patient with antihistamines or nebulizer)	80%
Moderate respiratory symptoms (treated in medical office or emergency department)	84%
Severe respiratory symptoms (requiring hospitalization)	100%
Asthma and sinus disease in the absence of exposure to NSAIDs	42%
Daily aspirin therapy (81 mg) for cardiovascular prophylaxis; desensitization with first exposure‡	Unlikely

- Oral ASA challenge in 836 Korean subjects with asthma
- History of previous ASA reaction single best predictor of AERD (specificity: 92.0%, NPV: 94.1%)  
(Chang HS, et al. *Allergy Asthma Immunol Res* 2011;3:256-264.)

# Diagnostic Considerations

- Oral ASA challenge in following scenarios:
  - Patients who have not used NSAIDs recently
  - Patients on leukotriene-modifying drug
  - Patients less perceptive to their reactions (Grade IV polyps)
  - Patients already on daily low-dose ASA



- 76% (100/131) positive on nasal challenge
- 82% (14/31) positive with oral challenge
- 17 true negatives

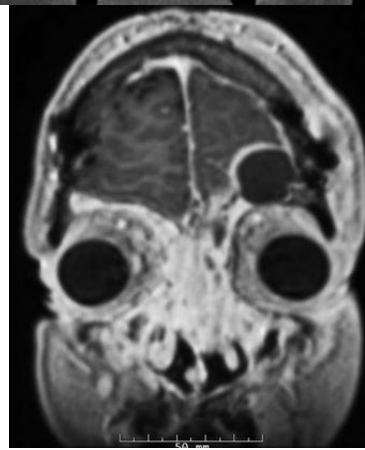
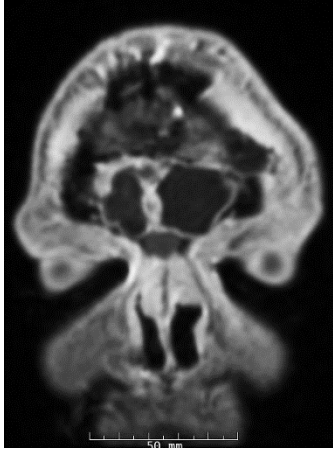
# Management of AERD: Considerations

1. Comprehensive FESS +/- ?Lothrop
2. High-dose steroid irrigations and EDS-FLU
3. ASA desensitization
4. Leukotriene modifying agents
  - Montelukast (Singulair®), zileuton (Zyflo CR®)
5. Biologics
  - Dupilumab (Dupixent®), omalizumab (Xolair®), mepolizumab (Nucala®)

# Surgical Philosophy in AERD

1. High rate of recidivism in this group!!!
2. “Full-house” FESS important for long-term disease control
3. Consider endoscopic modified Lothrop for recalcitrant frontal disease
4. Ongoing medical therapy postop and close follow-up are absolute requisites
5. **Surgical decision-making largely based on Grade III/IV studies**

# Patient Case

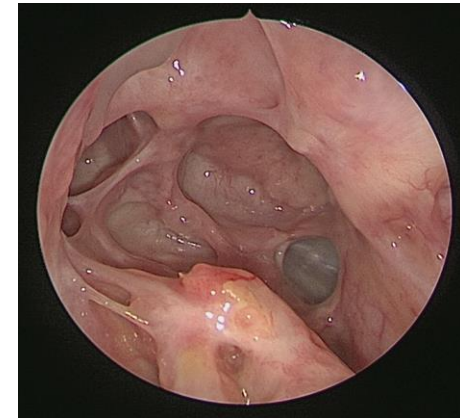
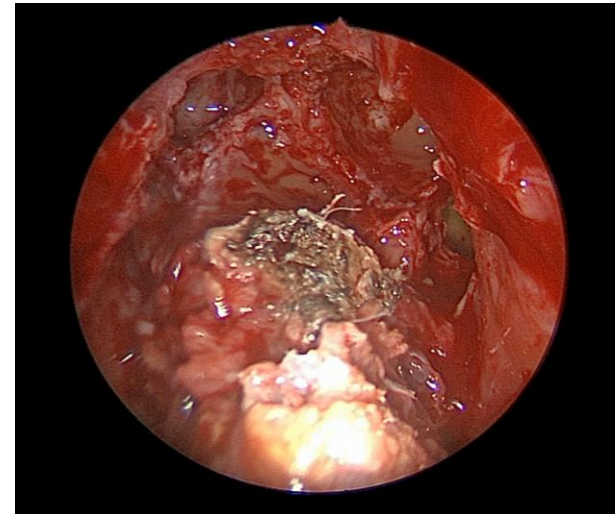


- 44 y/o male with CRSwNP
- Inhalant allergies, asthma, and AERD
- Previous FESS with frontal sinus obliteration



# Patient Case

- Comprehensive FESS with EML (2017)
- Mometasone irrigations twice daily
- Slow prednisone taper
- Montelukast 10mg daily
- ASA desensitization at 6 weeks (650mg bid)
- Dupilumab 300mg subQ q2weeks initiated (2022)

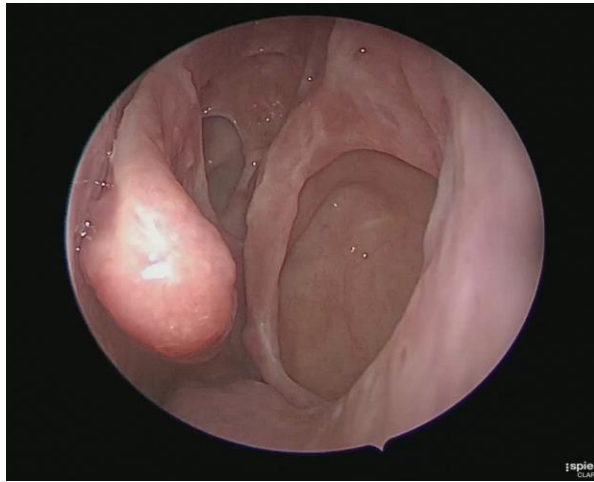


24 months

# FESS in AERD: Outcomes

- Systematic review of 18 studies
- FESS improves SNOT-22 scores and olfaction
- Improves asthma severity scores, decreased ER visits and hospitalizations, and reduced need for inhaled and oral steroid use
- ***Aggregate evidence suggests AERD patients more likely to have polyp recurrence, more likely to undergo revision surgery earlier and with increased frequency***

# EMLP in AERD: Outcomes



- 31 AERD patients
- Average F/U 36 months
- Polyp recurrence in 18 patients (58%)
- 7 patients required revision EMLP following initial surgery -- failure rate of 22.5%

# ASA Desensitization: Indications

- Rapidly recurring polyps following ESS
- Uncontrolled rhinosinusitis despite medical therapy
- Need for frequent bursts of oral steroids to control respiratory or sinus symptoms

**TABLE IV.** Indications and contraindications for an aspirin desensitization and aspirin therapy in patients with AERD

**Indications**

Persistent sinonasal and asthma symptoms in a patient with AERD despite conventional medical and surgical therapy

**Contraindications**

Poorly controlled asthma

Significant nasal polyp burden at time of desensitization

Pregnancy

History of eosinophilic esophagitis

History of gastric and/or peptic ulcer disease

History of a bleeding disorder or coagulopathy

History of medication nonadherence

**Relative contraindication**

History of anaphylaxis to aspirin or other NSAID\*

# ASA Desensitization: Early Data

- 65 AERD patients
- OAC followed by desensitization
- Daily treatment for 1 – 6 years (mean 3.1 years)
  - Sinus infections: 6 → 2/year ( $p < 0.0001$ )
  - Oral steroids: 10.2 → 2.5 mg ( $p < 0.0001$ )
  - Asthma hospitalizations 0.2 → 0/year ( $p < 0.0001$ )
  - Topical steroids: 139 → 106  $\mu\text{g}$  ( $p = 0.01$ )
  - Reduction of need for FESS ( $p = 0.004$ )

**Table 1**  
**Double-blind placebo-controlled trials of aspirin treatment after desensitization in patients with N-ERD**

Author	# of Patients Evaluated	ASA Maintenance Dose	Duration of Treatment	Effect of ATAD on Rhinosinusitis	Effect of ATAD on Asthma
Stevenson et al, <sup>32</sup> 1984	25 (both ASA and placebo in a crossover study)	325–1300 mg and 2600 mg	3 mo	Lower total nasal symptom score; no improvement in smell	No change in asthma symptom scores or prednisone maintenance doses
Fruth et al, <sup>34</sup> 2013	ASA, 18; Placebo, 13	100 mg	36 mo	Lower nasal symptom score, including improvement in smell; tendency for decreased relapse rate of nasal polyps	Not assessed
Świerzczyńska et al, <sup>33</sup> 2014	N-ERD: ASA, 8; Placebo, 7 Aspirin tolerant: ASA, 5; Placebo, 8	624 mg	6 mo	Lower nasal symptom score, no improvement in sinus involvement	Decrease in dose of ICS; improved asthma control No change in asthma symptom scores or FEV <sub>1</sub>
Esmailzadeh et al, <sup>35</sup> 2015	ASA, 18; Placebo, 16	1300 mg	6 mo	Lower nasal symptom score, improvement in sinus involvement	Lower asthma symptom scores, improvement in FEV <sub>1</sub>

- **Aggregate body of retrospective and prospective data supports efficacy of ASA desensitization**
- Wide variability in desensitization protocols
- Chronic ASA ingestion required to derive ongoing benefit (325-650mg bid)
- Adverse GI effects obstacle to long-term success....
- 6-18% discontinue ASA due to dyspepsia, abdominal pain, gastritis, or intestinal bleeding

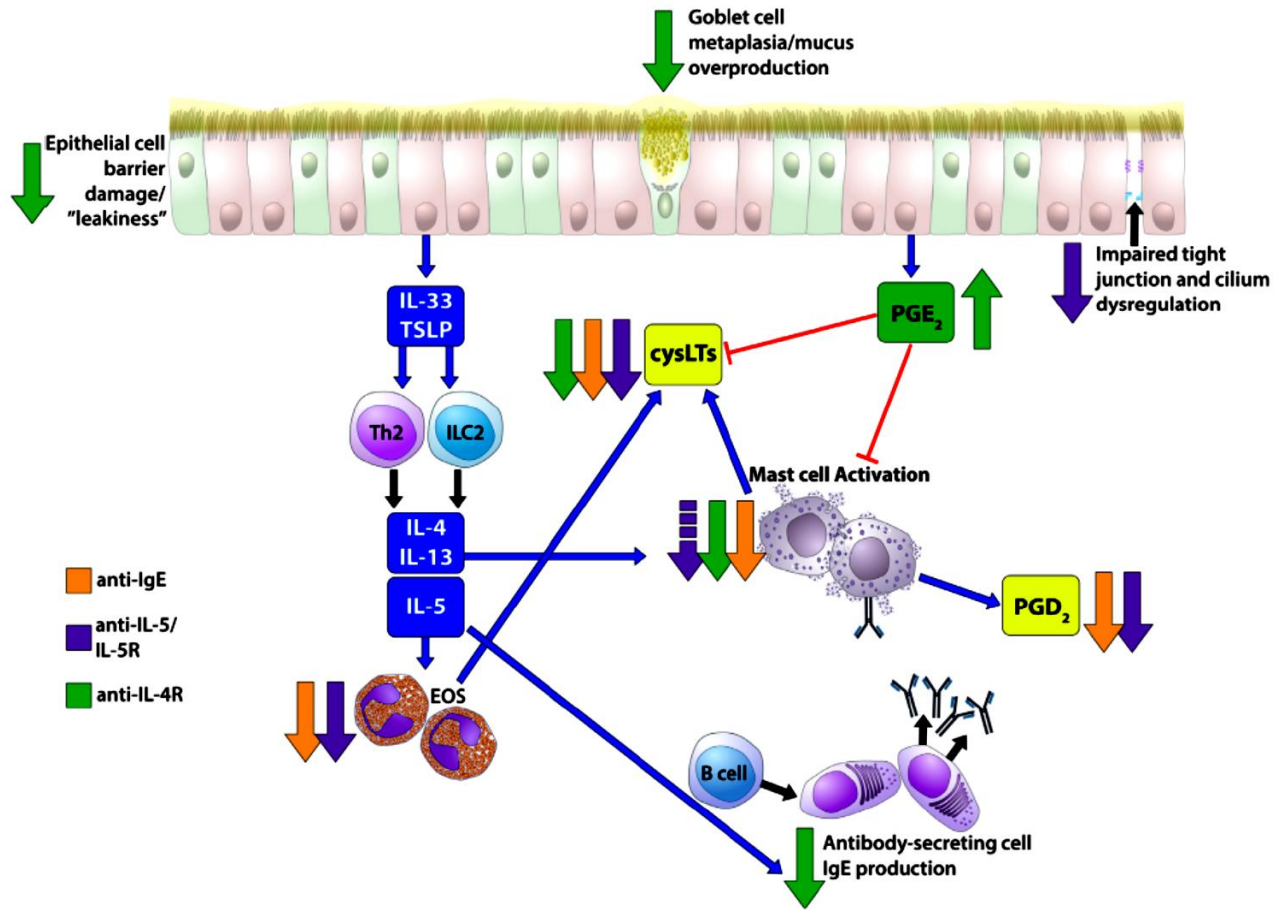
# Biologics in AERD: Outcomes Data

**Table 1**

Summary of Outcomes From AERD Subgroup Analyses From Phase III Studies of Dupilumab, Mepolizumab, and Omalizumab for Treatment of CRSwNP

Drug/target	US FDA–approved indications	AERD participants in phase 3 CRSwNP studies (AERD/total # participants, percentage)	Primary outcomes from phase 3 CRSwNP studies	AERD subgroup analyses of phase 3 CRSwNP data
Omalizumab/IgE	Asthma, CRSwNP, chronic spontaneous urticaria	72/265 (27.2%)	Treatment arm mean differences at week 24: NPS: - POLYP 1: -1.14 (95% CI: -1.59 to -0.69; $P < .0001$ ) - POLYP 2: -0.59 (95% CI: -1.05 to -0.12; $P = .0140$ ) NCS: - POLYP 1: -0.55 (95% CI: -0.84 to -0.25; $P = .0004$ ) - POLYP 2: -0.50 (95% CI: -0.80 to -0.19; $P = .0017$ ) <sup>86</sup>	Adjusted mean difference in NCS, NPS, SNOT-22, and UPSIT change from baseline at week 24 favored omalizumab vs placebo in both patients with AERD and aspirin-tolerant CRSwNP <sup>87</sup>
Mepolizumab/IL-5	Asthma, CRSwNP, EGPA, HES	108/407 (27%)	Adjusted difference in median at week 52: NPS: -0.73 (95% CI -1.11 to -0.34) Nasal obstruction VAS: -3.14 (95% CI -4.09 to -2.18) <sup>88</sup>	Mepolizumab led to reduction in NPS, nasal obstruction VAS, need for surgery, and use of systemic corticosteroids in both patients with AERD and aspirin-tolerant CRSwNP <sup>89</sup>
Benralizumab/IL-5R $\alpha$	Asthma	121/413 (29.2%)	Least squares mean change vs placebo at week 40: NPS: -0.57 (95% CI, -0.852 to -0.289; $P < .001$ ) NBS: -0.270 (95% CI, -0.458 to -0.083; $P < .005$ ) <sup>90</sup>	
Dupilumab/IL-4R $\alpha$	Asthma, CRSwNP, eosinophilic esophagitis, atopic dermatitis, prurigo nodularis	204/724 (28.2%)	Least squares mean difference vs placebo at week 24: NPS: Sinus 24: -1.80 (95% CI: -2.43 to -1.69; $P < .0001$ ) Sinus 52: -2.06 (95% CI: -2.10 to -1.51; $P < .0001$ ) NCS: - Sinus 24: -0.87 (95% CI: -1.03 to -0.71; $P < .0001$ ) - Sinus 52: -0.89 (95% CI: -1.07 to -0.71; $P < .0001$ ) <sup>91</sup>	Patients with AERD had significantly greater improvements with dupilumab than did aspirin-tolerant patients with CRSwNP for: nasal congestion, SNOT-22 scores, TSS, and PNIF. <sup>92</sup>

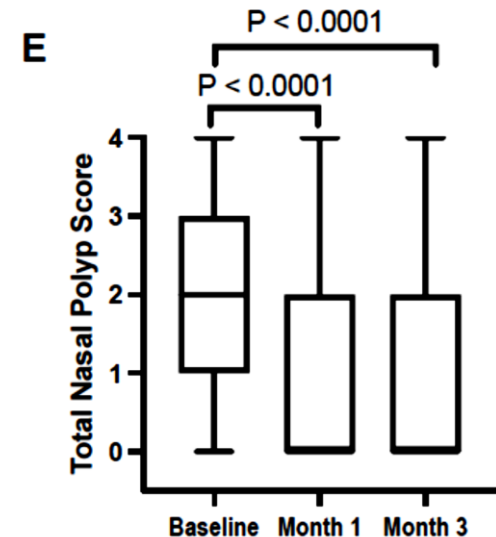
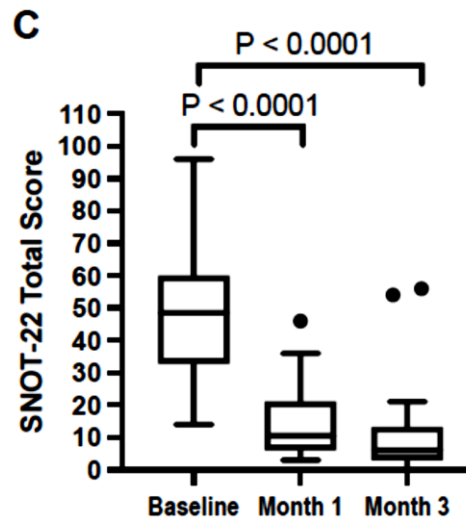
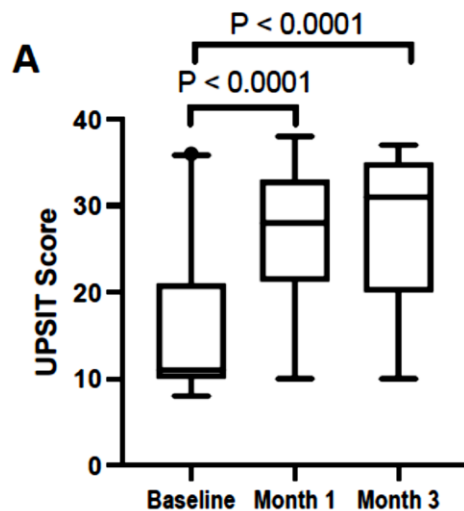
# Biologics in AERD: Mechanism of Action





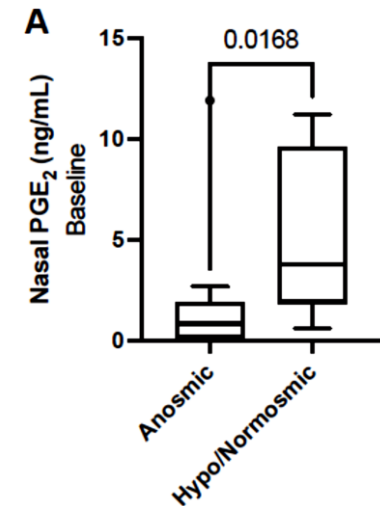
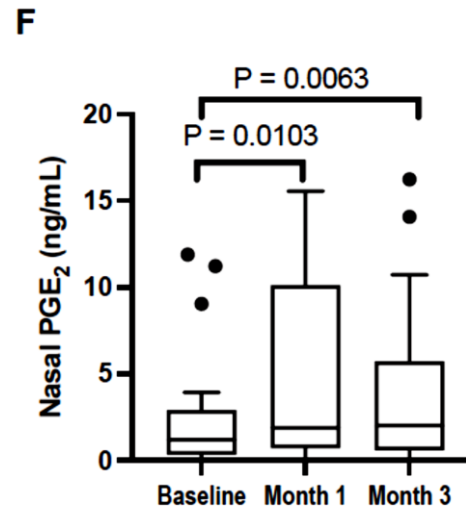
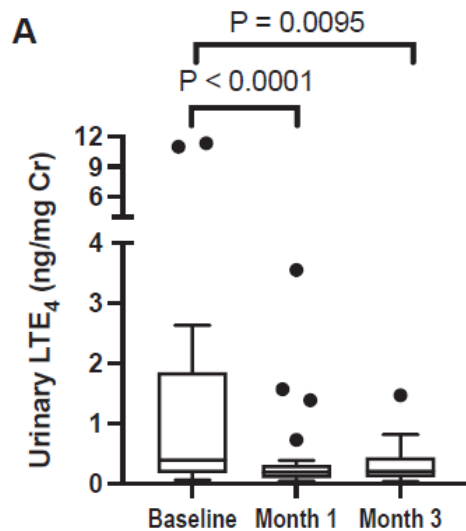
## Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease

- 22 patients with AERD
- Dupilumab for 3 months for severe asthma and/or CRSwNP
- Clinical outcomes assessed at baseline, 1 and 3 months



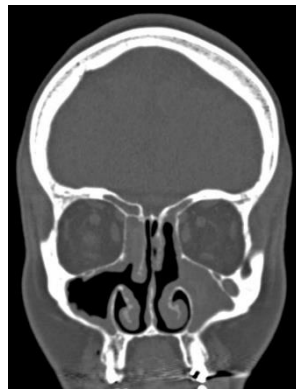
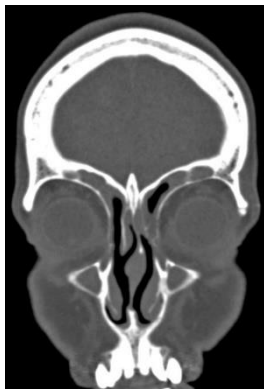
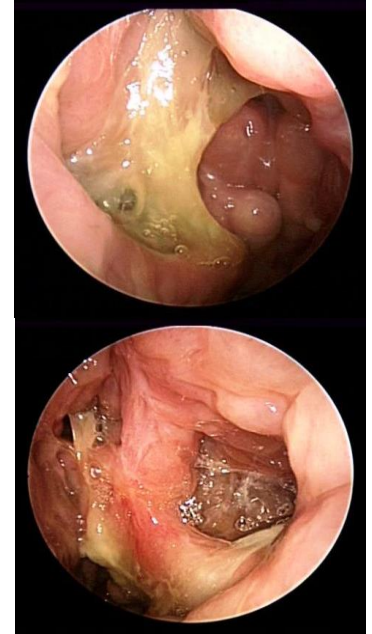
## Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease

- Dupilumab increased nasal PGE<sub>2</sub> levels
- Decreased nasal and urinary leukotriene E<sub>4</sub>
- Transcripts related to epithelial dysfunction and leukocyte activation and migration were downregulated in IT tissue



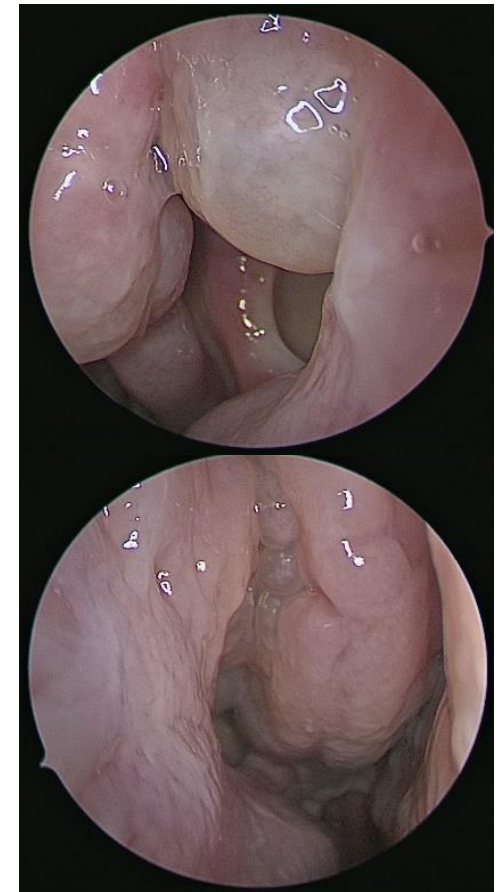
# Patient Case

- 42 y/o female with 5-year h/o protracted sinus issues (2014)
- Negative allergy testing and immune w/u
- Asthma and AERD
- 3 previous sinus surgeries



# Patient Case

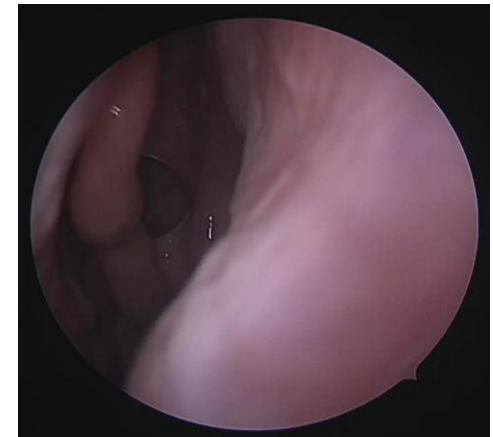
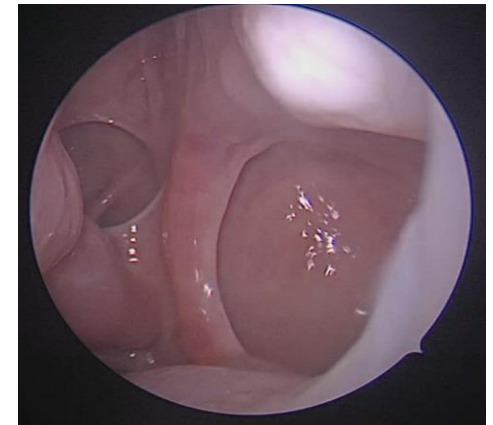
- Full-house FESS (2015) with clearing of polyps and eosinophilic debris
- Structured histopathology with high tissue eosinophilia and eosinophil aggregates
- Slow prednisone taper
- Continued zileuton, montelukast, and budesonide irrigations
- **Relapse at 1 year with progressive symptoms**



# Patient Case

- 2016: omalizumab, oral itraconazole
- 2017: levofloxacin/mometasone irrigations
- 2018: office polypectomy/steroid implants
- 2018: Nucala injections for asthma
- **March 2019: transitioned to dupilumab**
  - **Improvement with 2 doses**
- Maintained on dupilumab q2 weeks
- Montelukast and saline irrigations
- SNOT-22 score: 6/110 (January 2023)

**March 2019**



**January 2023**

# Final Thoughts

- 10% of polyp and 15% of severe asthma patients have AERD
- Associated with recalcitrant, severe disease
  - Higher burden of sinus disease
  - High rate of recurrence after surgery
- Optimal patient management includes comprehensive FESS and ongoing medical therapy
- ASA desensitization and biologics are key adjuncts for long-term disease control

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# Thanks!



# Questions?