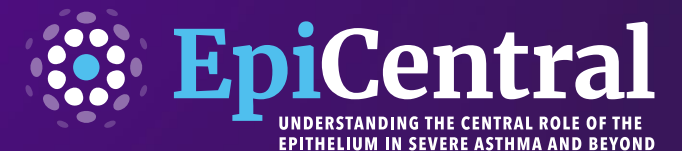




Additional phenotypes of chronic rhinosinusitis: AERD and AFRS

Learn more about the role of the epithelium in different
phenotypes of chronic rhinosinusitis



AERD, aspirin-exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis

Aspirin-exacerbated respiratory disease (AERD) (1/3) or NSAID-exacerbated respiratory disease (N-ERD)

What is AERD?

- AERD is characterized by:^{1,2}
 - **Chronic eosinophilic rhinosinusitis**
 - **Nasal polyposis**
 - **Asthma**
 - Acute respiratory **reactions to NSAIDs** with COX-1 inhibitory activity
- NSAID ingestion triggers:^{2,3}
 - **Upper and lower airway symptoms** (eg rhinorrhea, coughing, and bronchospasm)
 - **Non-respiratory symptoms** (eg pruritus, abdominal pain, and vomiting)

Prevalence

- In a meta-analysis of 27 studies from 13 countries, including the USA, AERD was estimated to be present in about:^{4*}



14.9% of patients
with **severe asthma**



9.7% of patients
with **nasal polyps**



8.7% of patients
with **CRS**

- However, these could be underestimates; a US study of electronic health records identified that **12.4%** of individuals exhibiting characteristics of clinical AERD were **undiagnosed**^{5†}

Diagnosis

- Diagnosis is mainly based on **patient history** of at least one reaction to NSAIDs^{1,6}
- If history is unclear, **provocation challenge with NSAIDs** can confirm diagnosis^{1,6}
- A high proportion of patients with AERD also **experience alcohol-induced respiratory reactions**, awareness of which might prompt clinical investigation^{7,8}

*Prevalence rates obtained from a meta-analysis of clinical trials in adult patients with AERD published on or before June 16, 2013; †Suspected cases of AERD identified using an informatics algorithm to search electronic health records of patients (age ≥18 years) from 2004–2014. Confirmation of diagnosis and classification as diagnosed or undiagnosed were performed by two clinical experts independently
AERD, aspirin-exacerbated respiratory disease; COX-1, cyclooxygenase-1; CRS, chronic rhinosinusitis; N-ERD, NSAID-exacerbated respiratory disease; NSAID, non-steroidal anti-inflammatory drug
1. Dominas C, et al. Laryngoscope Investig Otolaryngol 2020;5:360–367; 2. Laidlaw TM. World J Otorhinolaryngol Head Neck Surg 2018;4:162–168; 3. Badrani JH, Doherty TA. Curr Opin Allergy Clin Immunol 2021;21:65–70;
4. Rajan JP, et al. J Allergy Clin Immunol 2015;135:676–681.e1; 5. Cahill KN, et al. J Allergy Clin Immunol 2017;139:819–825.e6; 6. Fokkens WJ, et al. Rhinology 2020;58(Suppl S29):1–464;
7. Cardet JC, et al. J Allergy Clin Immunol Pract 2014;2:208–213; 8. Ramos CL, et al. Ann Allergy Asthma Immunol 2023;131:382–384

Aspirin-exacerbated respiratory disease (AERD) (2/3) or NSAID-exacerbated respiratory disease (N-ERD)

Burden of disease

Disease severity

- A US study showed that, compared with patients with CRSwNP alone or CRSwNP and comorbid asthma, patients with AERD:¹



Had **more severe sinus disease**
(based on sinus mucosal thickening
observed on CT scans)



Underwent **more sinus surgeries**



Were more likely to have **OCS-dependent disease**

Burden of revision surgery

- Similarly, a UK audit identified that the prevalence of AERD was significantly higher in patients with CRS who had **undergone multiple sinonasal surgeries** compared with those who had not²

Quality of life

- Data suggest that patients with AERD, compared with CRSwNP alone or CRSsNP, suffer the **most burdensome symptoms**,³ and nasal congestion, anosmia, and hyposmia in particular impact their physical and mental health⁴

Risks of aspirin desensitization

- There is evidence that aspirin desensitization benefits patients with AERD by alleviating symptoms and improving lung function following 6 months of treatment⁵
- However, the treatment is also associated with an increased risk of adverse events including gastritis and gastrointestinal bleeding⁵

AERD, aspirin-exacerbated respiratory disease; CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; CT, computed tomography; N-ERD, NSAID-exacerbated respiratory disease;

NSAID, non-steroidal anti-inflammatory drug; OCS, oral corticosteroid

1. Stevens WW, et al. J Allergy Clin Immunol Pract 2017;5:1061–1070.e3; 2. Philpott C, et al. BMJ Open 2015;5:e006680; 3. Schneider S, et al. J Clin Med 2020;9:925;

4. Tchekmedyan R, et al. Clin Exp Allergy 2022;52:1414–1421; 5. Eraso I, et al. PLoS One 2021;16:e0247871

US-90447 Last Updated 6/24. © 2024 AstraZeneca. All Rights Reserved. This information is intended for healthcare professionals only. EpiCentral is sponsored by Amgen and AstraZeneca.

Aspirin-exacerbated respiratory disease (AERD) (3/3) or NSAID-exacerbated respiratory disease (N-ERD)

Pathology and the role of epithelial cytokines

- AERD consists of **chronic baseline inflammation** (presenting as asthma and nasal polyposis) and **acute hypersensitivity to COX-1 inhibitors**¹
- Both phases are associated with overproduction of **pro-inflammatory CysLTs** and **PGD₂**, and underproduction of **anti-inflammatory PGE₂**¹⁻³
 - The underproduction of **PGE₂** has been linked to chronic underexpression or reduced function of **COX-2** and/or **PGES**⁴
 - Ingested aspirin inhibits **COX-1**, thus compounding low levels of PGE₂ and accounting for aspirin-induced reactions⁴
- Epithelial-derived **TSLP**, **IL-33**, and **IL-25** are thought to contribute to AERD pathogenesis by driving a **Type 2 immune response**:^{3,5,6}
 - TSLP** and **IL-33** stimulate **mast cells** to produce **PGD₂**, which in turn recruits **eosinophils**, **basophils**, and **ILC2s** into the respiratory tissues^{5,6}
 - ILC2s** release **Type 2 cytokines IL-4**, **IL-5**, and **IL-13** which, in conjunction with **CysLTs** and **PGD₂**, promote bronchoconstriction, eosinophilic tissue inflammation, and mucus production³
 - Additionally, **PGD₂** is thought to cause acute swelling of the sinuses and airways, leading to nasal congestion¹

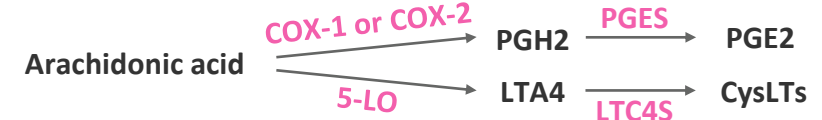


Figure 1. Arachidonic acid metabolism^{1,4}

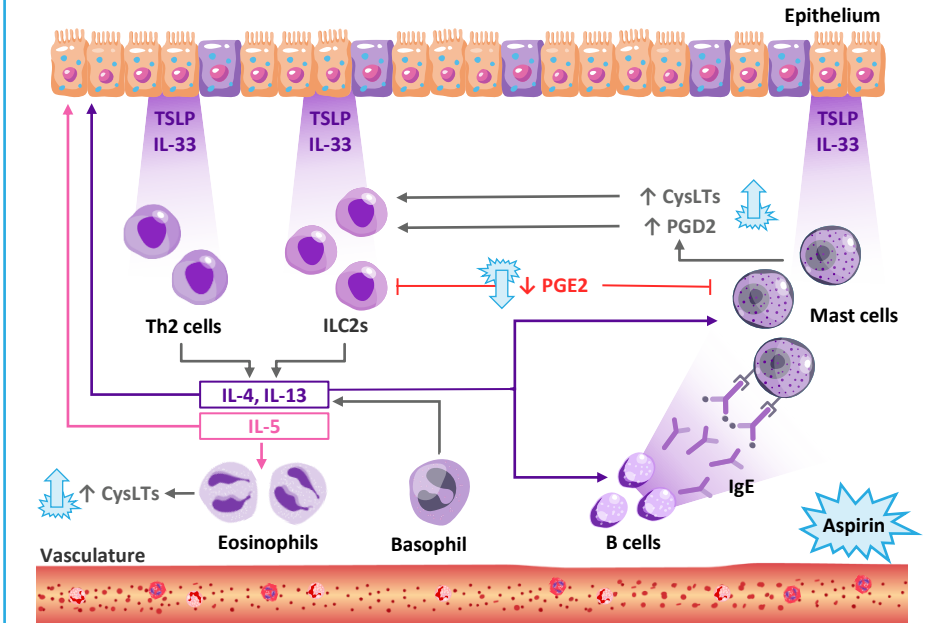


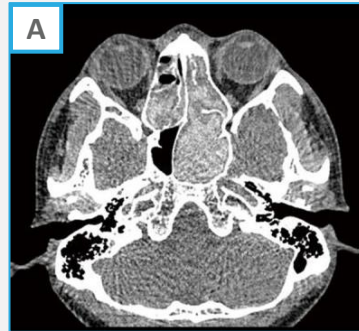
Figure 2. Pathways implicated in AERD pathogenesis^{3,4,6}

The information presented in these figures has been simplified for illustration purposes. Mechanisms underlying AERD require further elucidation, and the illustrated pathway is a hypothesis only
 5-LO, 5-lipoxygenase; AERD, aspirin-exacerbated respiratory disease; COX, cyclooxygenase; CysLT, cysteinyl leukotriene; IgE, immunoglobulin E; IL, interleukin; ILC2, Type 2 innate lymphoid cell; LTA4, leukotriene A4; LTC4S, leukotriene C4 synthase; N-ERD, NSAID-exacerbated respiratory disease; NSAID, non-steroidal anti-inflammatory drug; PGD₂, prostaglandin D₂; PGE₂, prostaglandin E₂; PGES, prostaglandin E synthase; PGH₂, prostaglandin H₂; Th, T helper; TSLP, thymic stromal lymphopoietin
 1. Laidlaw TM. World J Otorhinolaryngol Head Neck Surg 2018;4:162–168; 2. Dominas C, et al. Laryngoscope Investig Otolaryngol 2020;5:360–367; 3. Badrani JH, Doherty TA. Curr Opin Allergy Clin Immunol 2021;21:65–70; 4. Laidlaw TM, Boyce JA. J Allergy Clin Immunol 2023;151:301–309; 5. Buchheit KM, et al. J Allergy Clin Immunol 2016;137:1566–1576.e5; 6. Sehanobish E, et al. Curr Opin Allergy Clin Immunol 2022;22:42–48

Allergic fungal rhinosinusitis (AFRS) (1/2)

What is AFRS?

- AFRS is a subtype of **CRSwNP** characterized by intense **Type 2 inflammation** in response to **fungal colonization** in the sinuses¹
- Major diagnostic criteria include:^{1,2}
 - **Eosinophilic mucin**
 - **Absence of fungal invasion** in sinus tissue
 - **IgE-mediated hypersensitivity to fungi**
 - Characteristic **CT** imaging
 - **Fungi** on staining
- **MRI** also aids diagnosis: typically scans show central hypointensity on T1- and T2-weighted images, and signal void on T2-weighted images¹



CT (A) and MRI (B) scans of a patient with AFRS with bilateral involvement

Prevalence and risk factors

- In the European Position Paper on Rhinosinusitis and Nasal Polyps 2020, AFRS was reported to account for about **5–10%** of CRS cases²
- Patients are typically **atopic** and **immunocompetent young adults**¹
- Prevalence is higher in **warm and humid climates**, eg India and southern United States of America^{1,3}

Symptoms and burden

- Patients with AFRS present with symptoms of CRS that are **refractory to conventional medical therapy** and, notably, **thick tenacious nasal discharge**^{1,3}
- Patients with AFRS experience a high rate of revision surgeries, with a median interval of 2 years⁴
- Patients typically show **highly elevated serum total and fungal-specific IgE levels** compared with other CRSwNP subtypes³
- If untreated, complications such as visual disturbances, facial deformity, and bone erosion can occur¹

CT and MRI scans from Meng Y, et al. J Thorac Dis 2019;11:3569–3577

AFRS, allergic fungal rhinosinusitis; CRS, chronic rhinosinusitis; CRSwNP, CRS with nasal polyps; CT, computed tomography; IgE, immunoglobulin E; MRI, magnetic resonance imaging

1. Dykewicz MS, et al. J Allergy Clin Immunol 2018;142:341–351; 2. Fokkens WJ, et al. Rhinology 2020;58(Suppl S29):1–464; 3. Luong AU, et al. J Allergy Clin Immunol Pract 2022;10:3156–3162;

4. Philpott C, et al. BMJ Open 2015;5:e006680

Allergic fungal rhinosinusitis (AFRS) (2/2)

Pathology and the role of epithelial cytokines

- Fungal exposure can stimulate release of epithelial cytokines **TSLP**, **IL-25**, and **IL-33**, which drive downstream **Type 2 immune responses**:^{1,2}
 - **Th2** cells and **ILC2s** produce **IL-5**, which promotes eosinophilia; **Th2** cells produce **IL-4** and **IL-13**, which induce B cells to produce IgE, including anti-fungal IgE¹⁻³
- In-vitro evidence suggests that **epithelial permeability** is increased in patients with AFRS owing to decreased expression of tight junction-associated proteins⁴

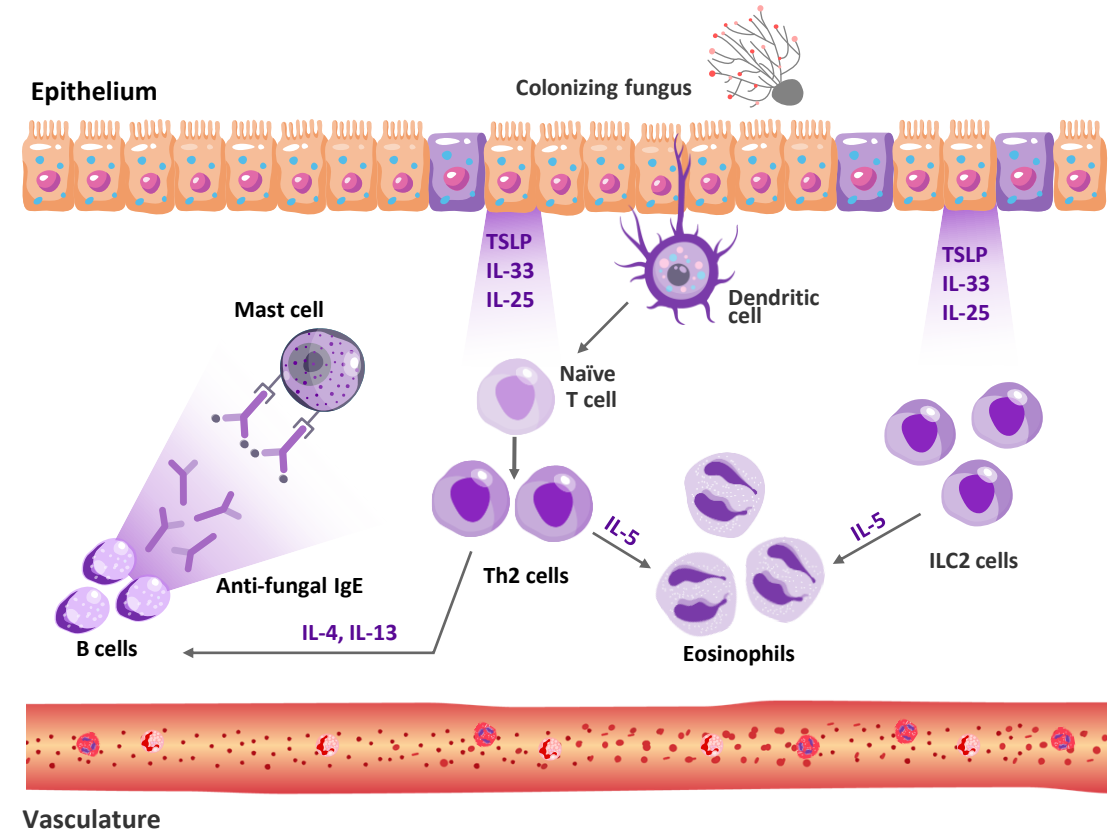


Figure adapted from Dykewicz MS, et al. J Allergy Clin Immunol 2018;142:341–351 and Luong AU, et al. J Allergy Clin Immunol Pract 2022;10:3156–3162

AFRS, allergic fungal rhinosinusitis; IgE, immunoglobulin E; IL, interleukin; ILC2, Type 2 innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin

1. Dykewicz MS, et al. J Allergy Clin Immunol 2018;142:341–351; 2. Shin S-H, et al. Int J Mol Sci 2023;24:2366; 3. Luong AU, et al. J Allergy Clin Immunol Pract 2022;10:3156–3162;

4. Den Beste KA, et al. Int Forum Allergy Rhinol 2013;3:19–25