Phenotypes of chronic rhinosinusitis

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

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UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND

Aspirin-exacerbated respiratory disease (AERD) (1/3)

or NSAID-exacerbated respiratory disease (N-ERD)

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What is AERD?

- AERD is characterised 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 rhinorrhoea, coughing and bronchospasm)
  - **Non-respiratory symptoms** (eg pruritus, abdominal pain, vomiting)

Prevalence

- AERD is 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 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 16 June 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; 5. Cahill KN, et al. J Allergy Clin Immunol 2017;139:819–825; 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

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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 not[2]

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 health[4,5]

Risks of aspirin desensitisation

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

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; 2. Philpott C, et al. BMJ Open 2015;5:e006680; 3. Schneider S, et al. J Clin Med 2020;9:925;
4. Tchekmedyian R, et al. Clin Exp Allergy 2022;52:1414–1421; 5. Claeys N, et al. Front Allergy 2021;2:761388; 6. Eraso I, et al. PLoS One 2021;16:e0247871

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Aspirin-exacerbated respiratory disease (AERD) (3/3)

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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 reactions[4]
- 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 production[3]
  - Additionally, **PGD2** is thought to cause acute swelling of the sinuses and airways, leading to nasal congestion[1]

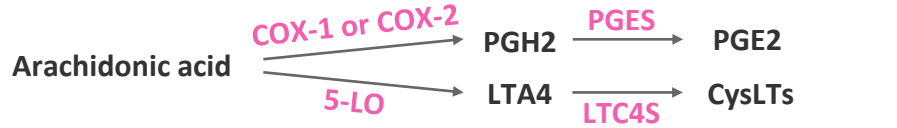

Figure 1. Arachidonic acid metabolism[1,4]

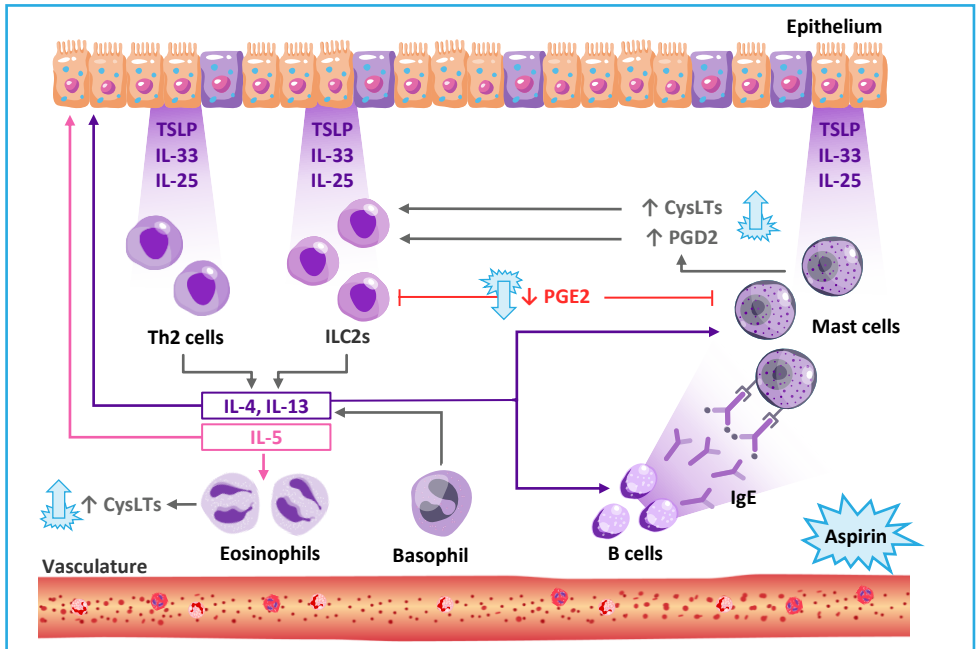

Figure 2. Pathways implicated in AERD pathogenesis[3,4,6]

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; 6. Sehanobish E, et al. Curr Opin Allergy Clin Immunol 2022;22:42–48

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Allergic fungal rhinosinusitis (AFRS) (1/2)

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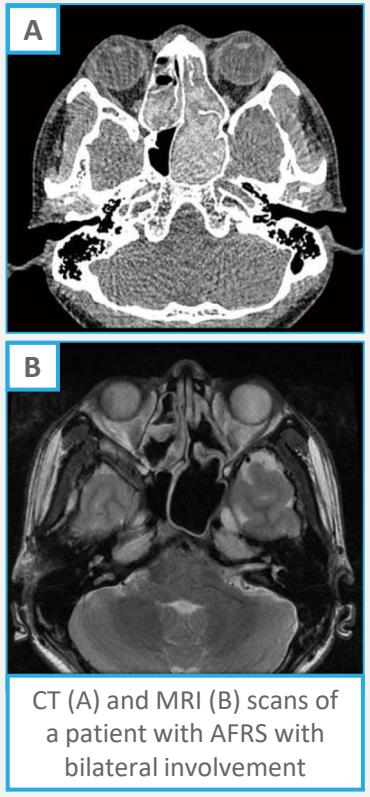
What is AFRS?

- AFRS is a subtype of **CRSwNP** characterised by intense **Type 2 inflammation** in response to **fungal colonisation** in the sinuses[1]
- 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
  - **Nasal polyposis**
- **MRI** also aids diagnosis: typically scans show central hypointensity on T1- and T2-weighted images, and signal void on T2-weighted images[1]



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

Prevalence and risk factors

- AFRS accounts for about **5–10%** of CRS cases[2]
- 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 years[4]
- Patients typically show **highly elevated serum total** and **fungal-specific IgE levels** compared with other CRSwNP subtypes[3]
- If untreated, complications such as visual disturbances, facial deformity and bone erosion can occur[1]

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. 29):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

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Allergic fungal rhinosinusitis (AFRS) (2/2)

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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 IgE[1,2]
- In-vitro evidence suggests that **epithelial permeability** is increased in patients with AFRS owing to decreased expression of tight junction-associated proteins[3]

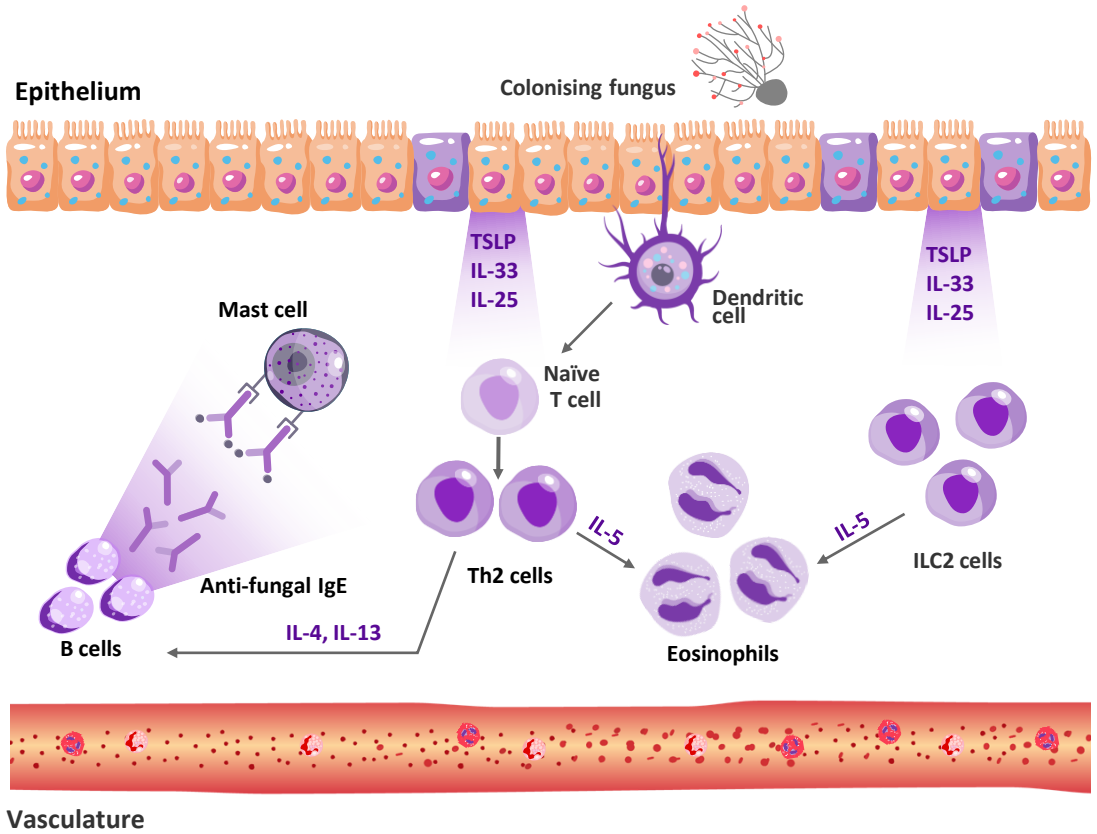

Figure adapted from Dykewicz MS, et al. J Allergy Clin Immunol 2018;142:341–351 and Luong AU, et al. J Allergy Clin Immunol Pract 2022;10:3156–3162
AFRS, allergic fungal rhinosinusitis; IgE, immunoglobulin E; IL, interleukin; ILC2, Type 2 innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin
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. Den Beste KA, et al. Int Forum Allergy Rhinol 2013;3:19–25

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