Personalised Treatment Approaches in Asthma

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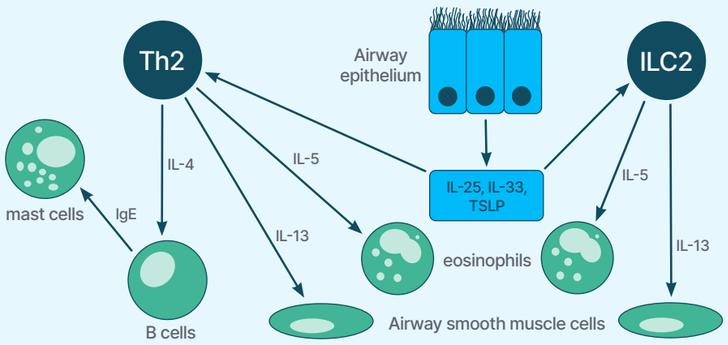
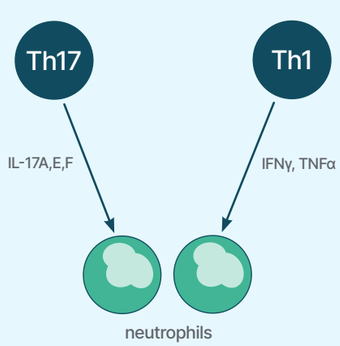
Heterogeneity of Asthma

- Asthma is a common, chronic, non-communicable disease affecting >260 million people globally, and responsible for >450,000 deaths each year[1]
- Asthma is heterogeneous in nature, with differences in **endotypes** and **phenotypes**
- In up to 10% of cases, patients are affected by severe asthma, defined as asthma that remains uncontrolled despite optimised high-dose ICS and LABA treatment
- **Endotypes** reflect immuno-pathophysiological mechanisms behind airway inflammation



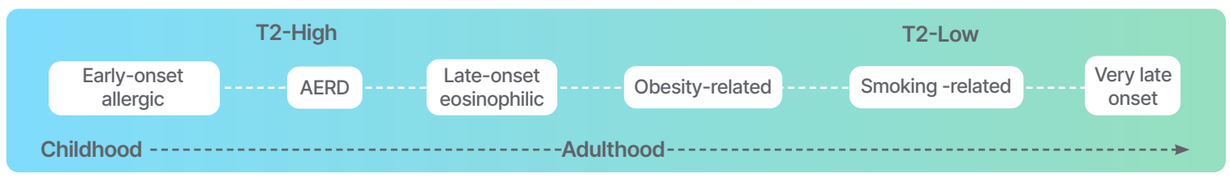


1. **T2-high asthma** is driven by Type 2 inflammation (IL-4, IL-5, IL-13), leading to eosinophilic inflammation. It accounts for ~60% of cases of SA and includes allergic asthma and non-allergic eosinophilic asthma[2-4]

2. **T2-low asthma** is characterised by either neutrophilic inflammation or a lack of significant granular inflammation (paucigranulocytic asthma)[2-4]

Phenotypes reflect clinical presentation[2,3,5]

- Early-onset allergic: atopic, childhood onset, mild-to-severe
- Late-onset eosinophilic: non-atopic, often with CRSwNP, often steroid-resistant
- AERD: adult-onset, nasal polyps, aspirin/NSAID sensitivity, typically severe
- Obesity-related: non-atopic, middle-aged females, often severe symptoms
- Smoking-related: older adults, frequent exacerbations, reduced lung function
- Very late onset: >50–65 years, linked with immunosenescence



Personalised Care: Where Are We Now?

While diagnostic biomarkers for T2-high asthma are now well established, specific biomarkers for T2-low asthma have yet to be identified. Similarly, biologics (mAbs) are revolutionising treatment for severe T2-high asthma, but identification of targeted therapies for T2-low asthma is an unmet need.

Biomarkers[1,2,4,6]

T2-high asthma

- Sputum eosinophils ≥2–3%
- FeNO ≥20 ppb
- Blood eosinophils ≥150–300/ µL
- Elevated serum total IgE, usually >100 IU/mL (allergic asthma)

T2-low asthma

- Absence of elevated T2-high markers
- Sputum neutrophils >60–76% (neutrophilic asthma)
- Neutrophils <76%; eosinophils <3% (paucigranulocytic asthma)
- Elevated IL-8/IL-17 in serum or sputum - emerging evidence[4]

Biologics[1,3,7,8]

- **Anti-IgE** (omalizumab) for severe allergic asthma
- **Anti-IL-5/Rα** (mepolizumab, reslizumab, benralizumab) for SEA ; benralizumab can also be used as a treatment of acute eosinophilic exacerbations[7]
- **Anti-IL-4Rα** (dupilumab) for severe T2-high asthma
- **Anti-TLP** (tezepelumab) targets upstream inflammation, making it a potential treatment option for patients with severe T2-high and T2-low asthma

Comorbidities:

- Benralizumab/dupilumab / mepolizumab: effective in SEA with nasal polyps (~60% of SEA cases)[8]
- Mepolizumab/benralizumab: benefit SEA with bronchiectasis (30–50% of SA cases)[8]

Management

- **Single maintenance and reliever therapy** (SMART) uses combined ICS-LABA in the treatment of asthma[9]
- Personalised asthma action plans now empower patients with tailored **self-management strategies**[10]

What's Next?

The treatment goal for asthma is shifting from symptom control to clinical remission, defined as "very mild or no asthma symptoms, no exacerbations, and no use of systemic corticosteroids for at least 12 months."[11]

Emerging priorities:

Early mAb use in mild T2-high asthma to prevent airway remodelling and disease progression[8]

Elucidating pathogenesis of T2-low asthma for biomarker and biologic discovery[6]

Multi-omics datasets (genomics, transcriptomics, proteomics, etc.) to refine endo-phenotype classification and identify potential new biomarkers[12]

Digital inhalers show promise for improving adherence, reducing inhaler errors, and avoiding medication overuse, but long-term data are needed[13,14]

Conclusion

- Personalised asthma treatment is transforming care by **targeting disease heterogeneity**
- **Biomarkers** guide therapy choices in T2-high asthma, and new **biologics** are improving patient outcomes
- Future advances aim for **clinical remission**, with smarter, data-driven, patient-centred management

Abbreviations:
AEC: airway epithelial cell; AERD: aspirin-exacerbated respiratory disease; CRSwNP: chronic rhinosinusitis with nasal polyps; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; ILC2: innate lymphoid cell type 2; IFN-γ: interferon gamma; LABA: long-acting beta agon mAb: monoclonal antibody; NSAID: non-steroidal anti-inflammatory drug; ppb: parts per billion; Rα: receptor alpha; SA: severe asthma; SEA: severe eosinophilic asthma; T2: Type 2; Th: T helper; TSLP: thymic stromal lymphopoietin.

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