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About the Author

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Dr. Mukherjee is an Assistant Professor in the Division of Respirology, Department of Medicine, and a translational scientist affiliated with the Research Institute of St. Joe's, Hamilton. She has demonstrated expertise in investigating inflammatory mechanisms of chronic respiratory diseases, in particular autoimmunity, response to treatment and development/validation of clinical biomarkers. Her research has identified the presence of localized autoimmune responses in the airways of patients with complex airways disease and determined their pathogenic role in driving disease severity. Of recent, she has identified autoimmune responses in acute-severe COVID and linked autoimmunity with post-acute COVID-19 sequelae (or Long COVID). In the field of respiratory medicine, she published ~65 manuscripts, and in the past 5 years these have accumulated >2500 citations (*Google Scholar h-index 24, i10-index 40*). Dr. Mukherjee's research program focuses on "Lung autoimmunity and biomarkers". She is a past recipient of the Emerging Researcher Award in Allergic Asthma awarded conjointly by the Canadian Institutes of Health Research (CIHR) and the Canadian Asthma, Allergy and Immunology Foundation (CAAIF). Her lab is funded by federal and non-federal sources including CIHR-ICRH and industry. Dr Mukherjee was recently named the AstraZeneca Chair in Respiratory Diseases (2023–2028).

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Pearls from the European Academy of Allergy and Clinical Immunology (EAACI) Congress, 2025

Manali Mukherjee, PhD

Introduction

The European Academy of Allergy and Clinical Immunology (EAACI) Congress 2025, held in Glasgow, Scotland, United Kingdom from June 13 to 16, centred on the overarching theme of "Breaking boundaries in Allergy, Asthma, and Clinical Immunology: Integrating Planetary Health for a Sustainable Future." Indeed, this year's theme emphasized the intersection of environmental health and allergic diseases. The vibrant congress featured several presentations on immunological diseases in both adult and pediatric populations, along with breakthroughs in clinical and translational domains. Key topics included asthma, allergy, chronic spontaneous urticaria, and current global challenges such as pollution and climate change. This report highlights several key studies, organized under three main themes: pediatric studies, biologics in combined airways disease, and biomarkers.

Pediatric Studies

Pediatric allergic diseases, including asthma, atopic dermatitis (AD), food allergies, and allergic rhinitis, are driven by dysregulated immune responses, often characterized by type 2 inflammation. Key immunologic features

include elevated immunoglobulin E (IgE) levels, eosinophilia, and cytokines such as interleukin (IL)-4, IL-5, and IL-13. Disease onset and progression are influenced by early-life exposures, genetic predisposition, and epithelial barrier dysfunction. Understanding immune endotypes in children is crucial for developing targeted therapies, including biologics. Recent advances highlight the role of epithelial-derived cytokines such as thymic stromal lymphopoietin and IL-33, offering new therapeutic avenues, particularly in pediatric asthma.[1] Precision medicine approaches are increasingly important in managing pediatric allergic diseases effectively and safely.

1. *Abstract:* Treatment of severe atopic dermatitis in pediatric patients with dupilumab and effects of therapy on nasal and skin microbiota: preliminary experimental evidence

This study was presented by Dr. Crisitiana Indolfi (Naples, Italy).

Atopic dermatitis (AD) is a common chronic inflammatory skin condition affecting up to 20% of children worldwide. Typically emerging in early childhood, it can significantly impair quality of life due to persistent itching, sleep disturbances, and emotional distress. Pediatric AD is frequently associated with immune dysregulation and skin barrier dysfunction, which predispose children to infections and allergic comorbidities. A recent study shows that in pediatric patients, *Staphylococcus aureus* colonization induces pruritus, barrier dysfunction, and inflammation, making AD management particularly challenging.[2] Severe cases may be resistant to conventional therapies, prompting the need for targeted biologics. As understanding of AD pathophysiology advances, treatments such as dupilumab are gaining prominence for their ability to modulate immune pathways and restore skin health in children.

This retrospective study evaluated the impact of **dupilumab** on clinical outcomes and microbial composition in children aged 6–16 years with moderate-to-severe **AD**. Thirty participants were divided into three groups: severe AD treated with dupilumab, moderate AD without biologics, and healthy controls. Nasal and skin swabs were analyzed via matrix-assisted laser desorption/ionization (MALDI)-time of flight (TOF) spectrometry for microbiota.

Results:

Over a 12 month period, dupilumab treatment led to significantly improved disease severity Eczema Area and Severity Index (EASI), itch intensity Numerical Rating Scale (NRS), and quality of life Children's Dermatology Life Quality Index (C-DLQI).

- **EASI:** Median score decreased from 24.5 to 1.2 at 12 months (P <0.001)
- **NRS:** Reduced from 10 to 3 (P <0.01)
- **C-DLQI:** Declined from 13.5 to 3.5 (P <0.1)

Untreated AD patients showed higher colonization compared to both dupilumab-treated patients and healthy controls. There was a significant reduction in *Staphylococcus aureus* colonization in skin and nasal cavities among dupilumab-treated patients (P <0.001), suggesting a restoration of microbial balance.

Key Takeaways:

Dupilumab is a safe and effective treatment for moderate-to-severe pediatric AD, offering substantial clinical improvement and restoring microbial balance. This groundbreaking pediatric study follows what has been identified in the adult population demonstrating that dupilumab modifies both nasal and skin microbiota in children, reducing infection risk and highlighting the therapeutic potential of biologics in managing complex AD cases.

2. *Abstract:* Primary and safety outcomes of a phase 3, open-label, single-arm, 12-week study of treatment with PI3Kδ inhibitor leniolisib in paediatric patients aged 4–11 years with activated PI3Kδ syndrome (APDS)

This study was presented as an oral abstract by Dr. M. Semeraro.

Leniolisib is an FDA-approved PI3Kδ inhibitor used to treat activated phosphoinositide 3-kinase delta syndrome (APDS)[3] in patients aged ≥12 years who weigh ≥45 kg. However, data on the safety and efficacy of leniolisib in pediatric patients (<12 years) remains limited. This

abstract, presented at EAACI by Drs. V.K. Rao and G. Uzel, reported findings from a phase 3, open-label, single-arm study that evaluated the safety and efficacy of leniolisib, in pediatric patients aged 4–11 years diagnosed with APDS—a rare genetic immunodeficiency marked by lymphoproliferation and immune dysregulation. Conducted across multiple international sites, the trial enrolled 21 children who received weight-adjusted doses of leniolisib twice daily for 12 weeks. The study met its co-primary endpoints: a reduction in lymph node size and a significant increase in naïve B cells, indicating improved immune regulation. Secondary outcomes included favourable changes in spleen volume and immunoglobulin levels. Importantly, leniolisib was well tolerated, with only mild to moderate adverse events reported, none of which led to treatment discontinuation.

Results:

After 12 weeks of leniolisib treatment across all dose levels:

- Mean change from baseline (CFB) in log10-transformed index lymph node sum of product of diameters (SPD) was –0.1956 (n=19).
- Mean CFB in naïve B cell percentage (CD19+, CD27-, CD10- out of total B cells) was 33.3%.
- Mean changes from baseline in immunoglobulin levels (n=14): IgM, 2.7 to 1.6 g/L; IgG, 10.1 to 11.1 g/L; and IgA, 0.88 to 0.83 g/L.
- Leniolisib was generally well tolerated: 20 patients had treatment-emergent adverse events, which were either Grade 1 (n=20, 95.2%) or Grade 2 (n=8, 38.1%); none were serious. No adverse events and no discontinuations of study treatment occurred.

Key Takeaways:

This pediatric trial builds on earlier adult and adolescent studies, including a placebo-controlled phase 3 trial published in *Blood*, which demonstrated similar efficacy and safety outcomes in older patients.[3] The consistent results across age groups supports leniolisib's potential as a targeted, disease-modifying APDS treatment. With more than 25% of APDS patients under 12, this study addresses a crucial unmet need in pediatric immunology. A trial in children aged 1–6 years is underway, and regulatory submissions for broader pediatric approval are expected.

Biomarkers

Biomarkers are increasingly recognized as essential tools in asthma management, enabling personalized approaches to diagnosis, monitoring, and treatment. They help identify key inflammatory pathways—particularly type 2 inflammation—guiding the use of targeted biologics. As asthma is now understood to be a heterogeneous disease, biomarkers such as blood eosinophils and fractional exhaled nitric oxide (FeNO) are gaining prominence in patient stratification and predicting therapeutic response. While these markers have improved outcomes, especially in moderate-to-severe asthma, their benefits remain modest, underscoring the need for more precise biomarkers that reflect the actual lung pathology. This urgency was evident at EAACI 2025, where the importance of biomarker-driven patient selection was a recurring theme, and several promising new biomarkers were presented in key studies.

3. *Abstract:* Baseline type 2 biomarkers and mucus plug response in patients with uncontrolled moderate-to-severe asthma treated with dupilumab in the VESTIGE study

This study was presented by Dr. Arnoud Bourdin (*Montpelier*).

Mucus plugging is a cardinal feature of fatal asthma.[4] Elevated mucus scores, indicated by luminal plugging on computed tomography (CT) scans in patients with moderate-to-severe asthma, are associated with chronic airway inflammation driven by type 2 cytokines—particularly IL-13, which contributes to excessive mucus production and airway obstruction. Given its role in disease severity and symptom burden, mucus is currently under extensive investigation as a treatable trait in asthma.[5] Dupilumab, a monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signalling, was evaluated in the phase 4 VESTIGE study (NCT04400318) for its impact on mucus burden. The primary results were published in *Lancet Respiratory Medicine*, (March 25;13(3):208-220; PMID: 39947221). This post hoc analysis assessed changes in mucus plug score and volume in patients stratified by baseline levels of type 2 inflammatory biomarkers, including FeNO and blood eosinophil counts. In this randomized, double-blind trial, 109 adults

with uncontrolled asthma and elevated type 2 inflammation received either dupilumab or placebo biweekly for 24 weeks. Changes in mucus plug score and volume from baseline to Week 24 were analyzed in patient subgroups categorized by initial FeNO levels (<50 or ≥50 ppb) and eosinophil counts (<400, ≥400, or ≥500 cells/μL). Mucus plug scores were determined from pre-bronchodilator multidetector CT scans, which measured the number of bronchopulmonary segments that were completely blocked (on a scale from 0 to 18). Mucus volume was quantified using voxel-based imaging analysis of all visible mucus plugs.

Results:

- At Week 24, dupilumab significantly reduced mucus plug scores compared to placebo across all biomarker subgroups.
- The effect was consistent regardless of FeNO levels (<50 or ≥50 ppb) and across stratification based on blood eosinophil counts (especially in patients with counts ≥400 and ≥500 cells/μL).
- Patients with lower eosinophil counts (<400) also showed numerical improvements.
- Mucus plug volume, measured using voxel quantification from CT scans, decreased significantly at Week 24 in the dupilumab group compared to placebo.
- The least squares mean difference in mucus volume was approximately −0.107 mL for dupilumab versus placebo (p <0.001), indicating a robust treatment effect.

Key Takeaways:

Dupilumab significantly reduced mucus plug scores and volumes compared to placebo across all biomarker subgroups, regardless of FeNO levels or eosinophil counts. These findings suggest that dupilumab effectively reduces mucus burden in asthma patients with type 2 inflammation, reinforcing its potential role in targeting mucus as a modifiable trait in asthma management.

4. *Abstract:* Basal serum tryptase: sex-and age-specific reference intervals in the pediatric and adult population

This study was presented by Y. Chantran (Paris, France).

Mast cells are increasingly recognized as central players in the pathophysiology of allergic diseases and asthma. These immune cells release a variety of mediators, including histamine, tryptase, and cytokines, which drive inflammation, bronchoconstriction, and tissue remodelling. Their activation contributes to both immediate hypersensitivity reactions and chronic airway inflammation. In asthma, mast cells are often located in close proximity to airway smooth muscle, influencing disease severity and response to therapy. Emerging research expands the role of mast cells beyond traditional allergy paradigms, highlighting their importance in asthma endotyping and identifying novel therapeutic targets. Their relevance continues to grow in precision medicine and biomarker development.

Tryptase is often used as a biomarker of mast cell activity. Indeed, baseline serum tryptase (bST) serves as a key biomarker in clonal mast cell disorders and is a minor diagnostic criterion for systemic mastocytosis. Elevated bST levels are also associated with increased risk and severity of hypersensitivity reactions and are linked to Hereditary alpha-Tryptasemia (HαT). Traditional reference values for bST have been challenged, prompting the need for age- and sex-specific reference intervals (RIs) to improve diagnostic accuracy and clinical decision-making in in mast cell-related disorders and allergy. The aim of the study was to define and validate age- and sex-specific RIs for bST from infancy through old age, and to develop an accessible, user-friendly online tool in order to assist physicians and pathologists in interpreting bST values of their patients.

Method:

A training cohort consisting of 21,216 bST values from a nation-wide ambulatory community-based clinical database in France was used to compare five indirect methods for establishing bST RIs. The most accurate method was then applied to determine age- and sex-specific bST RIs. These were validated in a separate cohort of 572 HαT-positive adolescents from a population-based birth study. Mucus plug scores and volumes were assessed using CT-based voxel quantification.

Key Results:

- Across all age and sex groups, the median and 95th percentile bST values were 4.6 µg/L and 8.4 µg/L, respectively.
- bST levels declined from infancy through puberty, then gradually increased with age.
- Females consistently exhibited lower bST levels than males, particularly during adolescence and early adulthood.
- In the validation cohort, 4.9% (28/572) of participants exceeded the 95th percentile for their age and sex.
- A free, user-friendly online tool was developed to help physicians and pathologists interpret patient bST values using age- and sex-specific percentiles.

Key Takeaways:

This study establishes validated, age- and sex-specific reference intervals for bST from infancy through old age and introduces a practical online tool to support clinical interpretation. These findings enhance the precision of bST-based diagnostics for mast cell-related disorders and allergic conditions. An unmet need remains for evaluating tryptase levels in blood and sputum of patients with asthma and allergy, indicating the importance of developing detection methods and validated reference intervals. This study forms a stepping stone toward addressing this unmet need.

Update on Biologics in the Combined Airways: Adult Studies

In addition, several sessions discussed asthma and rhinosinusitis as components of a unified airway disease, with a focus on phenotypes and inflammatory molecular endotypes. This concept of a combined airways disease/unified disease is rooted in the understanding that the respiratory tract functions as a unified system, where inflammation in one region often affects the other. This combined airway disease is increasingly recognized as a distinct clinical phenotype, particularly in patients with type 2 inflammation, where shared immunological pathways (e.g., IL-4, IL-5, and IL-13) drive disease in both the nose and lungs. A holistic approach, rather than managing these conditions as separate entities, can improve symptom control, reduce exacerbations, and enhance quality of life. An interesting plenary talk by Dr. Brian Lipworth (University of Dundee, Scotland) addressed "Head-To-Head Comparison of Biologic Efficacy in Asthma: What Have We Learned", now published in *Allergy* (PMID: 40156481).[6]

5. *Abstract:* Efficacy of two years of treatment with anti-IL-5/R therapy for reduction in use of oral glucocorticoids in patients with eosinophilic granulomatosis with polyangiitis

This study was presented by Dr. Florence Roufosse (Paris, France).

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare inflammatory disease characterized by eosinophilia, vasculitis, and asthma. Sinus disease and severe asthma are two of the six diagnostic criteria and frequently occur together in affected patients. Standard treatment involves oral glucocorticoids (OGCs) and immunosuppressants, which carry significant toxicity and relapse risk. Targeted anti-IL-5/receptor therapies—**mepolizumab** and **benralizumab**—address eosinophilic inflammation and have shown efficacy in inducing remission. The MANDARA trial[7] compared these therapies over 52 weeks, followed by a 1-year open-label extension (OLE) in which all patients received benralizumab. Full results are now published (2025) (PMID: 40781045).[8]

This phase 3 randomized, double-blind trial followed by a one-year OLE evaluated the long-term efficacy and safety of anti-IL-5/receptor therapies in adults with relapsing or refractory EGPA. A total of 128 participants were enrolled, with 66 continuing benralizumab treatment and 62 switching from mepolizumab to benralizumab. Key endpoints included the proportion of patients achieving remission—defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and an OGC dose ≤4 mg/day—alongside relapse rates, blood eosinophil counts, patterns of OGC use and withdrawal, and safety outcomes including adverse events.

Results:

- The remission rates were comparable at Week 104: 62.1% (benralizumab/benralizumab) vs. 67.7% (mepolizumab/benralizumab). Approximately 50% of patients who achieved early remission maintained it through 2 years.
- During the first year of OLE, 77.3% (benralizumab/benralizumab) and 67.7% (mepolizumab/benralizumab) experienced no relapses.
- Most relapses were airway-related.
- Complete withdrawal of OGC was achieved by ~44% of patients in both groups by Week 104, with median cumulative OGC doses reduced by ~61–62% in year 2 compared to year 1.
- Blood eosinophil counts remained low (median ~20 cells/µL) in both groups, and switching to benralizumab led to further eosinophil depletion.

Key Takeaways:

Benralizumab provides durable remission, significant reduction in glucocorticoid use, and sustained eosinophil depletion over 2 years in EGPA patients. Switching from mepolizumab to benralizumab seemed to maintain the clinical benefits and low biomarker levels in a significant proportion of patients. However, supporting benralizumab as a foundational therapy in EGPA management remains inconclusive.

6. *Abstract:* Tezepelumab reduces OCS use and improves sino-nasal symptoms in OCS-dependent patients with severe asthma and comorbid chronic rhinosinusitis (overall and with nasal polyps): results from the phase 3b WAYFINDER study

This study was presented by David Jackson (United Kingdom).

Tezepelumab is a monoclonal antibody that blocks thymic stromal lymphopoietin, a key epithelial cytokine involved in initiating airway inflammation. Unlike other biologics, it acts upstream in immune pathways, offering potential efficacy across multiple asthma phenotypes. Approved for severe asthma, it also shows promise in broader airway disease management. Chronic rhinosinusitis (CRS), with or without nasal polyps (NP), frequently coexists with severe asthma. The WAYFINDER study (NCT05274815) evaluated the impact of tezepelumab on OCS reduction and sino-nasal symptoms in OCS-dependent asthma patients, including those with CRS.

The original study was a 52-week, open-label, single-arm trial. Adults with severe asthma on maintenance OCS received tezepelumab 210 mg every 4 weeks. The co-primary endpoints included achieving a reduction in OCS dose to ≤5 mg/day or complete discontinuation, without loss of asthma control. Sino-nasal symptoms were assessed using the Sino-Nasal Outcome Test-22 (SNOT-22) score.

Key Results:

- Reduction of OCS to ≤5 mg/day was achieved in 87.8% of patients with CRS overall and 91.7% of those with chronic rhinosinusitis with nasal polyps (CRSwNP).
- Complete discontinuation of OCS occurred in approximately 46% (CRS overall) and 50.0% (CRSwNP).
- Mean SNOT-22 scores improved by 15.7 points (CRS) and 18.9 points (CRSwNP) with approximately half of patients in both groups classified as SNOT-22 responders.

Key Takeaway:

Tezepelumab effectively reduces OCS dependence and improves sino-nasal symptoms in patients with severe asthma and CRS, supporting its role in managing combined airway disease.

Summary

Several sessions at this year's European respiratory congress at Glasgow, UK highlighted promising new therapies and biomarker-based treatment guidance strategies for both adult and pediatric populations, with a focus on treating multiple modalities of immunological diseases. The meeting also highlighted studies on mental health and public monitoring of diseases. The next annual meeting, marking the 70th anniversary, will take place in Istanbul, Turkey, from June 12–15, 2026.

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Financial Disclosures

M.M: None declared.

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