Moving the dial on identifying endotypes of asthma from early life

Lucy Perrem [1,2,3] and Padmaja Subbarao [1,2,4]

[1]Division of Respiratory Medicine, The Hospital for Sick Children, Toronto, ON, Canada. [2]Department of Pediatrics, University of Toronto, Toronto, ON, Canada. [3]Translational Medicine Program, SickKids Research Institute, Toronto, ON, Canada. [4]The Department of Medicine, McMaster University, Hamilton, ON, Canada.

Corresponding author: Padmaja Subbarao (padmaja.subbarao@sickkids.ca)

Shareable abstract (@ERSpublications)
There is a need for stable biomarkers of endotype for asthma across the lifecourse to provide earlier precision medicine approaches https://bit.ly/3PAS19i

Cite this article as: Perrem L, Subbarao P. Moving the dial on identifying endotypes of asthma from early life. *Eur Respir J* 2022; 60: 2201031 [DOI: 10.1183/13993003.01031-2022].

Received: 19 May 2022
Accepted: 15 Aug 2022

No longer recognised as a single disease entity with a "one size fits all" approach to treatment, asthma is an umbrella diagnosis spanning different endotypes and clinical phenotypes. The discovery of T2 inflammation as a driver in many asthma patients transformed our understanding of this disease and inspired the discovery of targeted biological therapies [1]. T2 inflammation is mediated by cytokines including interleukin (IL)-4, IL-5 and IL-13, which then regulate the production of measurable biomarkers including IgE, blood and sputum eosinophils, and fractional exhaled nitric oxide (F_{eNO}) [2]. There is an increasing selection of monoclonal antibodies targeting different T2 inflammatory pathways [3]. Tailored treatment strategies, including biologics, and potentially microbiome-based therapeutics [4], have the potential to alter the course of the disease. However, individualising therapy in clinical practice requires appropriate classification systems and accurate thresholds for biomarkers across different age groups [3]. Beyond these practicalities, there is still much to learn about asthma phenotypes and their evolution across the age spectrum.

In this issue of the *European Respiratory Journal*, Maison *et al.* [5] investigated the feasibility of applying a uniform classification system for identifying T2-high asthma that was age-independent using routine biomarkers such as blood eosinophil counts and allergen-specific IgE antibodies. This prospective multicentre German cohort study included data from 500 asthma patients (>6 years of age), 276 children aged <6 years with preschool wheeze and 349 healthy controls; participants were categorised into four mutually exclusive asthma phenotypes based on blood eosinophil counts and allergen-specific serum IgE antibodies: "atopy-only", "eosinophils-only", "T2-high" (eosinophilia and atopy) and "T2-low" (neither eosinophilia nor atopy). The authors of this study are to be commended for obtaining comprehensive epidemiological and physiological data from participants across the age spectrum.

The major finding of this study was that the T2-high phenotype asthma was identified across all ages with the highest prevalence in children and adolescents (40.2%) followed by adults (24.6%) and preschool children (16.9%). A high degree of environmental and food allergen sensitisation, reflected by the sum of all allergen-specific IgEs, was a key feature of the T2-phenotype across all ages, even when compared to the "atopy-only" subgroup. Notably, alternate classifications in adults for F_{eNO} >35 ppb and sputum eosinophils >3% led to similar prevalence of T2-high classification (26.7%). However, as the overlap between the definitions for adults was only 20%, the alternate classification systems may be complementary.

The clinical characteristics associated with the T2-high phenotype were age-dependent and inconsistent. In adults, although the T2-high phenotype was associated with a high exacerbation rate, the "eosinophils-only" phenotype was associated with the highest exacerbation rates per year and the greatest

proportion of severe asthmatics. Furthermore, the classification systems were unable to identify clinically severe subgroups amongst the paediatric or preschool age groups. Of note, the prevalence of the phenotypes varied by age, with the eosinophils-only phenotype almost exclusively seen in children <3 years, and adults over 60 years; while T2-high groups were highest amongst those 6–45 years of age. As the authors of this study acknowledge, most of the study participants were treated with long-term corticosteroids, including 22.3% of the adult cohort on regular oral corticosteroids. This may have impacted the test results and hence biased the phenotype categorisation.

An alternate explanation is the longitudinal shift in phenotype that is age-dependent.

Researchers have previously delineated different phenotypes based on the longitudinal trajectories of preschool wheeze, which take into account a life-course approach to changing symptoms, applying data-driven statistical approaches to large birth cohorts [6, 7]. We know that preschoolers with a persistent wheeze phenotype have a high probability of being diagnosed with asthma at 5 years of age [7]. Higher eosinophil level and low lung function are also predictive, but on an individual level, heterogeneity persists and it is difficult to prospectively distinguish children whose symptoms will remit or persist. Some of the most novel findings from this study by Maison *et al.* [5] were in the youngest age group. They showed a clear age dependency in the phenotypes, T2-high phenotype becoming the prominent phenotype in older preschool children (mean 4 years); while the T2-low and eosinophils-only phenotypes were the predominant forms in very young children <3 years of age. Although it is tempting to hypothesise that the phenotypes evolve from T2-low to atopy and later T2-high, the paper only has data on the stability of phenotypes over 2 years which is insufficient to assess longitudinal trajectories in this age group.

The early and accurate prediction of which preschoolers will be diagnosed with asthma at school-age is valuable because it allows for earlier intervention and preventative strategies. Researchers have developed clinical prediction models for the persistence of asthma based on early childhood wheezing episodes and other clinical variables [8, 9]. Maison *et al.* [5] showed that the proposed biomarker classification system had utility in the prediction of asthma diagnosis and symptom persistence over the follow-up period. They show that not only is the persistence of the T2 phenotype likely in the preschool period but those with the T2-high phenotype are very likely to be diagnosed with asthma at school age (n=15; 73.3%). By comparison, nearly 50% (n=36) of the T2-low group had remission of symptoms. It is unclear whether the addition of other biomarkers such as F_{eNO} in this age group would add complementary value to identifying T2 subgroups as shown in the adult data. Nonetheless, routine and clinically available biomarkers, such as blood eosinophils and allergy testing, provide predictive and phenotypic information and could facilitate individualised precision diagnosis in this challenging age group.

Blood eosinophil cell counts are relatively easy to obtain in all age groups and they remain the most established biomarker to distinguish T2-high from T2-low asthma [10]. A finding of this study was the higher cut-off (90th percentile) for eosinophils in healthy children ($\geqslant$470 cells·μL^{-1}) compared with adults ($\geqslant$360 cells·μL^{-1}). Reclassifying children using cut-offs for blood eosinophilia cited in trials of Th2 biologics (*e.g.* $\geqslant$150 and $\geqslant$300 cells·μL^{-1}), significantly changed the prevalence of asthma phenotypes, highlighting that these lower cut-offs do not accurately distinguish Th2-high children. More research is needed to identify clinically relevant thresholds for eosinophils to increase the accuracy of phenotyping and, in turn, the prescription of biologics targeting T2 inflammatory pathways.

There is no established definition of T2-high phenotypes in clinical practice or epidemiological studies and the biomarkers used to phenotype asthmatics are highly variable and easily influenced by environmental triggers or treatments [11]. Maison *et al.* [5] used a clinically informed approach to classify asthmatics into four groups. It would be interesting to understand whether data-driven agnostic approaches may also identify similar cut-offs or further improve the diagnostic capability for these varied biomarkers to identify asthmatic preschool children earlier and more precisely.

Another advantage of a data rather than a hypothesis-driven approach to phenotyping as used in other studies may have provided additional insights [11, 12] into the utility of combinations of biomarkers. A Danish cross-sectional study found that 70% of people with severe asthma demonstrated an increase in at least one T2 biomarker but only 15% had elevated F_{eNO}, IgE and blood eosinophils, concluding that co-expression of biomarkers was highly variable [10]. In contrast, Maison *et al.* [5] performed a sensitivity analysis in which adult patients were grouped using an alternate classification system of airway T2-high inflammatory classification, defined by F_{eNO} and sputum eosinophils. The overall prevalence of the T2-high phenotype was similar using both definitions but, on an individual basis, there was only a 20% overlap. The variable co-expression of the T2 biomarkers may be related in part to treatment used. These

results suggest that people should be categorised as having T2-high asthma based on at least one increased biomarker and that airway T2 inflammation cannot be accurately predicted based on serum markers alone [11].

The results of this study provide important insights into the prevalence and trajectories of asthma phenotypes in different age groups. The ALLIANCE cohort will certainly become increasingly useful over a longer follow-up period as the study participants age. The value in cohorts such as these is the opportunity to study the longitudinal utility of biomarkers in relation to disease symptom persistence, remission and response to therapy. This research furthers our understanding of asthma phenotypes longitudinally, which, in turn, may move the needle on integrating precision medicine into our care and improve our ability to earlier endotype this common disease.

Conflict of interest: L. Perrem reports advisory board honoraria from Sanofi. P. Subbarao reports grants from CIHR, Canada Research Chairs, Tier 1, Genome Ontario, Don and Debbie Morrison; participation on advisory board for OSMB NIH, outside of the submitted work.

References

1 Kuruvilla ME, Lee FE-H, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. *Clin Rev Allergy Immunol* 2019; 56: 219–233.
2 Chan R, RuiWen Kuo C, Lipworth B. Pragmatic clinical perspective on biologics for severe refractory type 2 asthma. *J Allergy Clin Immunol Pract* 2020; 8: 3363–3370.
3 Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med* 2022; 386: 157–171.
4 von Mutius E, Smits HH. Primary prevention of asthma: from risk and protective factors to targeted strategies for prevention. *Lancet* 2020; 396: 854–866.
5 Maison N, Omony J, Illi S, *et al.* T2-high asthma phenotypes across lifespan. *Eur Respir J* 2022; 60: 2102288.
6 Oksel C, Granell R, Haider S, *et al.* Distinguishing wheezing phenotypes from infancy to adolescence: a pooled analysis of five birth cohorts. *Ann Am Thorac Soc* 2019; 16: 868–876.
7 Dai R, Miliku K, Gaddipati S, *et al.* Wheeze trajectories: determinants and outcomes in the CHILD Cohort Study. *J Allergy Clin Immunol* 2022; 149: 2153–2165.
8 Chang TS, Lemanske RF, Guilbert TW, *et al.* Evaluation of the modified asthma predictive index in high-risk preschool children. *J Allergy Clin Immunol Pract* 2013; 1: 152–156.
9 Bose S, Kenyon CC, Masino AJ. Personalized prediction of early childhood asthma persistence: a machine learning approach. *PLoS One* 2021; 16: e0247784.
10 Frøssing L, Silberbrandt A, Von Bülow A, *et al.* The prevalence of subtypes of type 2 inflammation in an unselected population of patients with severe asthma. *J Allergy Clin Immunol Pract* 2021; 9: 1267–1275.
11 Lugogo NL, Akuthota P. Type 2 biomarkers in asthma: yet another reflection of heterogeneity. *J Allergy Clin Immunol Pract* 2021; 9: 1276–1277.
12 Howard R, Rattray M, Prosperi M, *et al.* Distinguishing asthma phenotypes using machine learning approaches. *Curr Allergy Asthma Rep* 2015; 15: 38.