

New innovations in allergy treatment and phenotyping

Food allergy is a reproducible, immune-mediated reaction to otherwise harmless food antigens. It can be elicited by micrograms or milligrams of antigenic proteins, resulting in typical symptoms such as urticaria (hives), angioedema, nausea, oropharyngeal pruritus, gastrointestinal and respiratory symptoms. In a proportion of individuals, food allergy can cause anaphylaxis.

The prevalence of food allergies varies significantly across populations and the condition can place a substantial health burden on those affected and their carers. Risk of developing food allergy is ascribed to the individual's genetic makeup and the exposome. In a genetically susceptible individual, lifestyle factors, diet and especially skin health have been associated with the induction of food allergies. Diagnosis is usually made by evaluating the clinical history after exposure to a relevant food, then using a skin-prick test or testing specific Immunoglobulin E (IgE) in the blood. Neither a skin-prick test nor antibody detection distinguishes well between those who are genuinely allergic and those who are sensitised without clinical reactivity. The gold standard method of diagnosing food allergy is through a double-blinded placebo-controlled food challenge. However, food challenges can be time-consuming and labour-intensive and need to occur in a medical setting with ready access to medical attention should an acute systemic reaction occur.

It is noteworthy that allergic reaction to some foods, especially egg, milk, wheat and soy can resolve spontaneously in early childhood, while others such as peanut, tree nuts and seafood allergies tend to persist. Until recently, avoidance has been the mainstay of food allergy management. In the case of non-severe allergic reactions, antihistamines can be used to reduce skin, nasal and eye symptoms. Increasing numbers of people with food allergy carry an adrenaline (epinephrine) autoinjector, since food allergy can rarely cause life-threatening anaphylaxis for which adrenaline is the standard treatment. Adrenaline acts through several mechanisms. The $\alpha 1$ adrenergic vasoconstrictor constricts blood vessels, increasing blood pressure to prevent shock. The $\beta 1$ -adrenergic receptor increases the heart rate, and $\beta 2$ -adrenergic effects reverse bronchoconstriction.

Last year, the US Food and Drug Agency and then the European Medicines Agency authorised the licensing of the first immunomodulatory treatment for food allergy, Palforzia. Although allergen immunotherapy has been used for over 100 years for treating inhalant allergies associated with rhinitis, conjunctivitis and asthma, initial attempts at subcutaneous allergen immunotherapy for food

allergy were unsuccessful. Palforzia is a peanut product administered through the oral route (oral immunotherapy, OIT) for treating people with peanut allergy. In contrast to immunotherapy for aeroallergens, which induces long-term clinical benefit after cessation of treatment, OIT is associated with only short-term sustained unresponsiveness to peanut while the treatment is continued. It is therefore topical that in this issue of *Clinical and Experimental Allergy*, Barshov and colleagues¹ present an extensive discussion of our current understanding of immune mechanisms of OIT. They report that OIT is associated with the induction of allergen-specific IgE and IgG4 antibodies with inhibitory activity, decreased allergen-induced basophil (in vitro) and mast cell (in vivo) hyporesponsiveness.^{2,3} A transient increase in Th2 and Th2A cells is followed by a deletion of pathogenic pro-allergic T cells. A likely explanation for this phenomenon is the induction of inducible IL-10+ Tregs and natural FoxP3+ Tregs. It remains unclear why some but not all who undergo OIT achieve sustained unresponsiveness. Therefore, it is essential to understand the underpinning mechanisms of sustained and unstained unresponsiveness following OIT to identify biomarkers of response and devise novel therapeutic strategies that would promote long-term sustained unresponsiveness (Figure 1).

Asthma is a complex chronic inflammatory disease marked with heterogeneity in clinical symptoms, severity and treatment response. It affects nearly 400 million people globally. Asthma severity varies from mild symptoms that are easily controlled to severe asthma with reduced quality of life, hospitalisation due to exacerbation and significant mortality risk. Severe asthma constitutes just 3–4% of asthma cases, and is defined as asthma that remains uncontrolled despite optimised treatment and good adherence to treatment. Patients often use high dose inhalation medication and are often steroid dependent. The current recognition of the underpinning clinical, inflammatory and molecular mechanisms of asthma has allowed the identification of several asthma phenotypes.⁴ In clinical practice, identifying asthma phenotypes has become more relevant for the choice of treatment, resulting in a personalised medicine approach to managing severe asthma patients.⁵ These asthma phenotypes can be clustered according to the inflammatory pathways, T2 high versus T2 low inflammation. The majority of severe asthma patients are characterised by T2 inflammation. In the Global Initiative for Asthma (GINA) guidelines, T2 inflammation includes elevated eosinophils, allergy, elevated fractional exhaled nitric oxide (FeNO) or the need for oral corticosteroids. Allergic asthma affects more

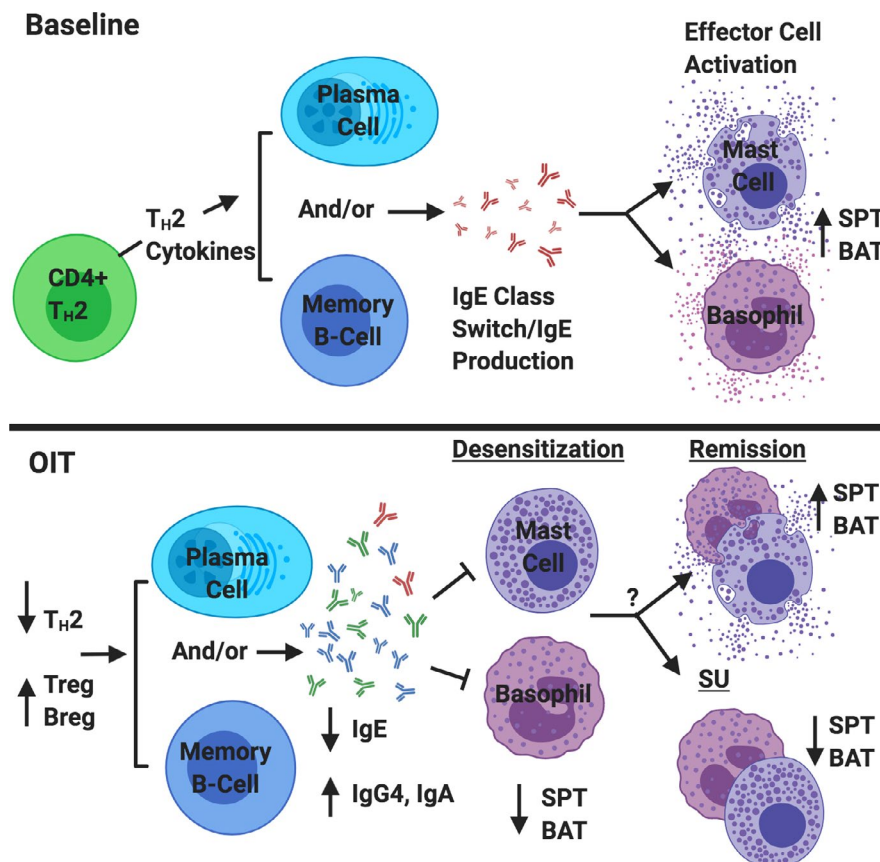


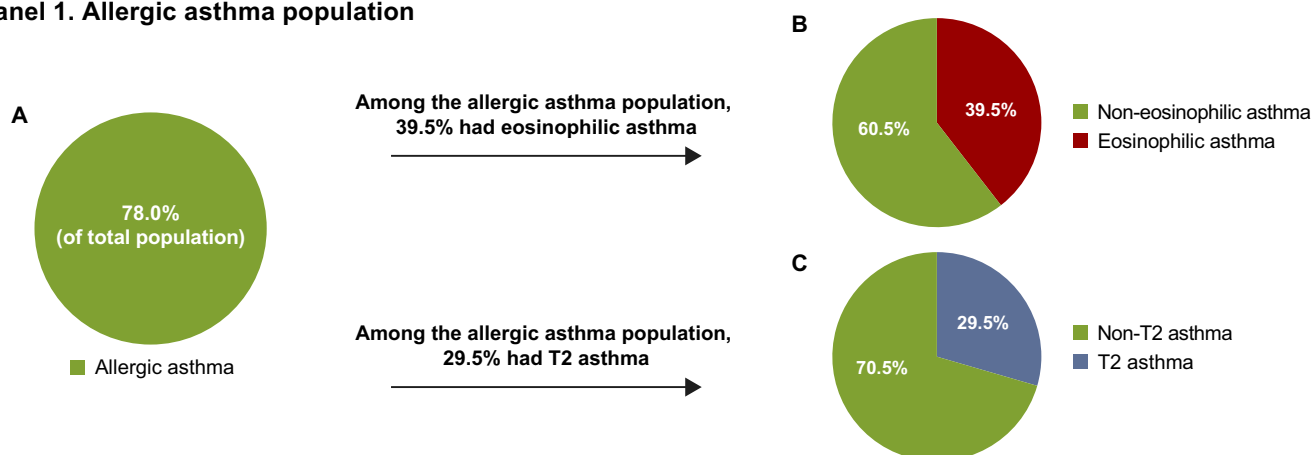
FIGURE 1 B-cell and effector cell responses in OIT. Baseline TH2 skewing in food allergic subjects results in IgE class-switching and specific IgE (sIgE) production, which binds to the high-affinity IgE receptor FcεRI on mast cells and basophils. Once primed with sIgE, mast cells and basophils rapidly degranulate on subsequent exposure to suprathreshold amounts of allergen, leading to an allergic response. This allergic state is characterized by elevated skin prick (SPT) wheal diameter and basophil activation (BAT). Oral immunotherapy (OIT) leads to decreased TH2 responses and increased regulatory responses, resulting in decreased production of sIgE and an increase in allergen-specific IgA (sIgA) and IgG4 (sIgG4). In desensitized subjects, sIgA and sIgG4 may function as blocking antibodies, preventing mast cell and basophil degranulation. It is unknown why some subjects experience loss of desensitization or remission, characterized by recurrence of clinical reactivity and loss of suppression of SPT and BAT, while some achieve sustained unresponsiveness (SU), characterized by the continued lack of clinical reactivity and suppression of SPT and BAT despite discontinuation of OIT

than half of patients with severe asthma. This endotype is characterised by increased immunoglobulin E (IgE) concentrations in serum following allergen exposure, eosinophilic airway inflammation and bronchial hyper-responsiveness. Eosinophilic asthma is associated with tissue and sputum eosinophilia, thickening of the basement membrane zone and corticosteroid refractoriness. In this journal last year, Kozlik et al reported a possible relationship between eosinophilia in broncho-alveolar lavage and collagen I accumulation in bronchial biopsy samples in adult with asthma.⁶ Both allergic and eosinophilic asthma groups can overlap and represent a broad T2 inflammatory pattern with allergy, eosinophilia and elevated FeNO. Nasal polyposis is often present, mainly in the eosinophilic and overlap phenotypes. Severe asthma with T2 inflammation can be treated with several biologicals; the choice of the biological is dependent on asthma phenotype. GINA 2020 guidelines present a helpful decision tree for the biological selection in type 2 asthma. Therefore, knowledge of phenotypes, including overlapping phenotypes, is very relevant for clinical practice. In general, it is important to determine the

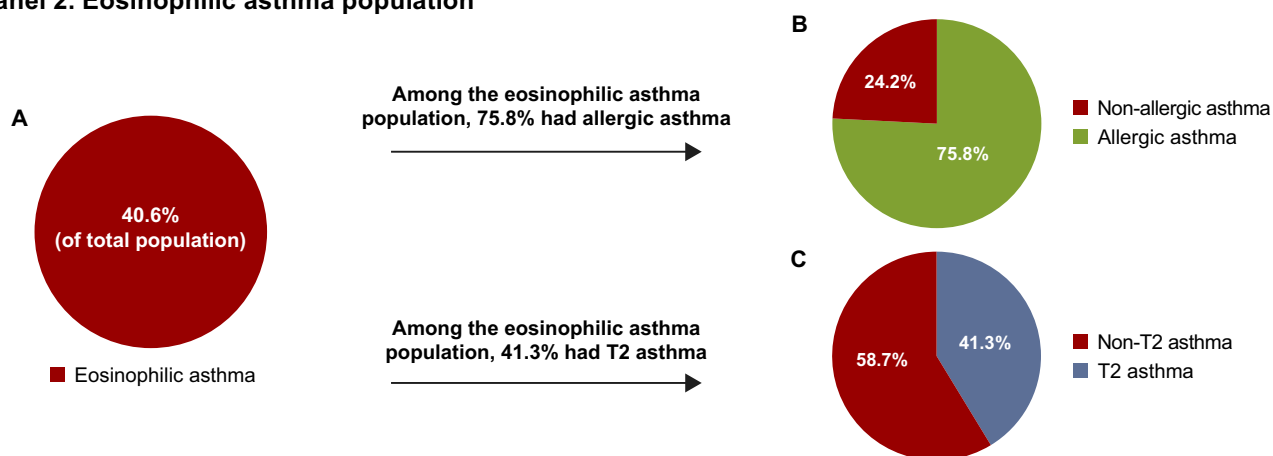
dominant pathway of inflammation resulting in uncontrolled asthma when selecting appropriate therapeutic options.

In this issue, Chen and colleagues⁷ have further defined the overlap among allergic, eosinophilic and type 2 asthma phenotypes. They performed *post hoc* analyses on baseline data in two adult cohorts, one not selected for any asthma subtype (N = 935), and the second was selected on the basis of allergic asthma (N = 1049). The level of overlap was assessed on the basis of skin prick-positive and/or positive serum-specific immunoglobulin E > 0.35 kU/L for allergic asthma and blood eosinophil high count ≥300 cells/μL and low cut-off ≥150 cells/μL for eosinophilic asthma. The authors used FeNO high level of ≥35 ppb and low cut-off of ≥25 ppb to selected local markers of type 2 inflammation and to limit overlap with the systemic eosinophilic asthma. The authors showed that in their cohort, allergic asthma was the most prevalent phenotype in adults with moderate-to-severe asthma followed by eosinophilic and type 2 asthma. As expected, there was considerable overlap between the different groups. The *post hoc* analysis shows that this classification

Panel 1. Allergic asthma population



Panel 2. Eosinophilic asthma population



Panel 3. T2 asthma population

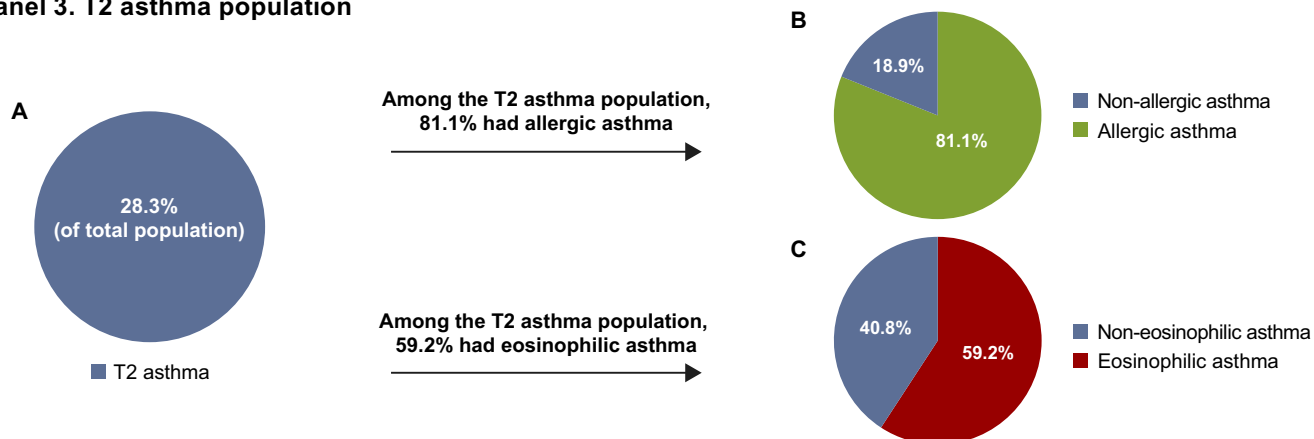


FIGURE 2 Overlap among (A) allergic, (B) eosinophilic and (C) T2 asthma subtypes in the non-subtype-selected population. Definitions: eosinophilic asthma, eosinophil count ≥ 300 cells/ μ L; T2 asthma, FeNO level ≥ 35 ppb. FeNO, fractional exhaled nitric oxide; T2, type 2

is relevant not only in severe but also in moderate asthma. This observation is very relevant since, also in moderate asthma patients, phenotyping may result in personalised treatment with improved patient outcomes (Figure 2).

In vitro diagnostic assays for measuring IgE concentrations to either allergenic extract or allergen components play an important role in supporting the diagnosis of allergic rhinitis.⁸ These assays also have the potential to be used for immune monitoring during allergen

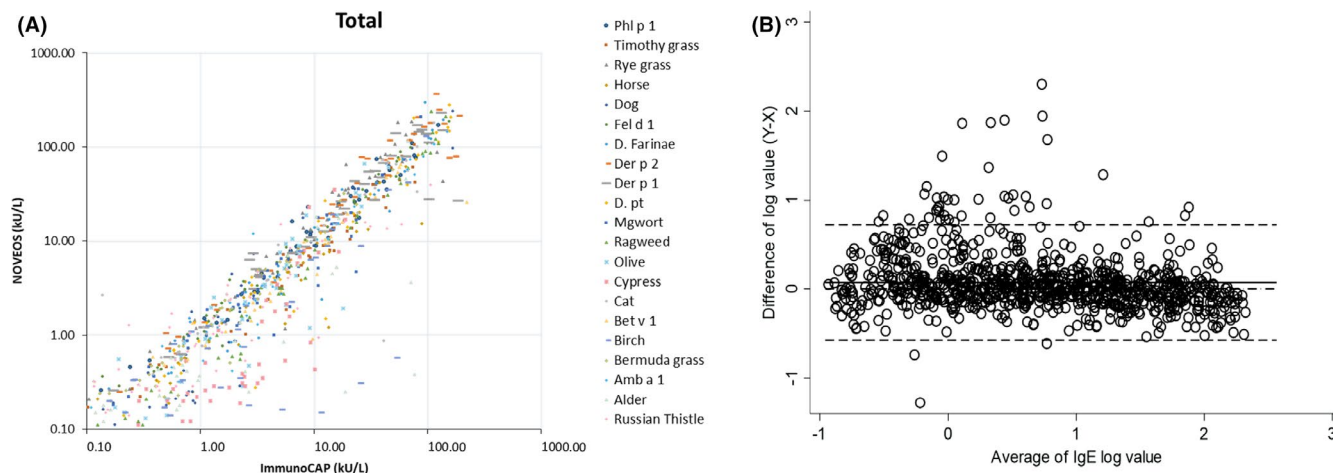


FIGURE 3 Correlation between the quantitative outcomes of NOVEOS vs ImmunoCAP IgE tests. (A) Scatter diagram; (B) Bland-Altman. In the Bland-Altman plot, the difference and the mean of the ImmunoCAP and the NOVEOS IgE log values (kU/L) are reported in the y- and x-axis, respectively. The continuous and the dashed lines parallel to the X-axis mark the population mean level and its bias, respectively, while the other two dash lines are the upper and lower limits of agreement, respectively

immunotherapy. Potapova and colleagues⁹ report the validation of an automated assay for IgE testing based on chemiluminescence detection and paramagnetic microparticles using small sample volume. The authors validated the method against the gold standard ImmunoCAP assay (Figure 3). Their singleplex NOVEOS system proved to be robust, reliable, and an alternative to the current ImmunoCap system when only a small volume of sample is available. Its utility in clinical practice remains to be further investigated.

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