Highlights and recent developments in airway diseases in EAACI journals (2018)

Jean Bousquet, Cezmi Akdis, Clive Grattan, Philippe Eigenmann, Karin Hoffmann-sommergruber, Ioana Agache, Marek Jutel

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REVIEW

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Highlights and recent developments in airway diseases in EAACI journals (2018)

Jean Bousquet[1,2,3,4] | Cezmi A. Akdis[5,6] | Clive Grattan[7] | Philippe A. Eigenmann[8] | Karin Hoffmann-Sommergruber[9] | Ioana Agache[10] | Marek Jutel[11]

[1]Fondation partenariale FMC VIA-LR, MACVIA-France, Montpellier, France

[2]INSERM U 1168, VIMA: Ageing and Chronic Diseases Epidemiological and Public Health Approaches, Villejuif, France

[3]UMR-S 1168, Université Versailles St-Quentin-en-Yvelines, Montigny le Bretonneux, France

[4]EUFOREA, Brussels, Belgium

[5]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

[6]Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland

[7]St John's Institute of Dermatology, Guy's Hospital, London, UK

[8]Pediatric Allergy Unit, University Hospitals of Geneva, Geneva, Switzerland

[9]Department of Pathophysiology, Medical University of Vienna, Vienna, Austria

[10]Department of Allergy and Clinical Immunology, Faculty of Medicine, Transylvania University Brasov, Brasov, Romania

[11]Department of Clinical Immunology, ALL-MED Medical Research Institute, Wroclaw Medical University, Wrocław, Poland

Correspondence
Jean Bousquet, CHRU Arnaud de Villeneuve, 371 Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France.
Email: jean.bousquet@orange.fr

Abstract

The European Academy of Allergy and Clinical Immunology (EAACI) supports three journals: Allergy, Pediatric Allergy and Immunology, and Clinical and Translational Allergy. EAACI's major goals include supporting the promotion of health, in which the prevention of allergy and asthma plays a critical role, and disseminating the knowledge of allergic disease to all stakeholders. In 2018, the remarkable progress in the identification of basic mechanisms of allergic and respiratory diseases as well as the translation of these findings into clinical practice were observed. Last year's highlights include publication of EAACI guidelines for allergen immunotherapy, many EAACI Position Papers covering important aspects for the specialty, better understanding of molecular and cellular mechanisms, identification of biomarkers for disease prediction and progress monitoring, novel prevention and intervention studies, elucidation of mechanisms of multimorbidities, introduction of new drugs to the clinics, recently completed phase three clinical studies, and publication of a large number of allergen immunotherapy studies and meta-analyses.

KEYWORDS

asthma, European Academy of Allergy and Clinical Immunology, rhinitis

1 | INTRODUCTION

The major goals of EAACI's three official journals - Allergy, Pediatric Allergy and Immunology, and Clinical and Translational Allergy are to support health education, in which allergy prevention and management play a critical role, and to disseminate the allergy knowledge to all stakeholders. The EAACI journals reported prognostic biomarkers, primary and secondary prevention of allergic diseases,

Abbreviations: AIRWAYS-ICPs, integrated care pathways for airway diseases; AR, allergic rhinitis; ARIA, allergic rhinitis and its impact on asthma; CHRODIS, chronic diseases and promoting healthy ageing across the life cycle; COPD, chronic obstructive pulmonary disease; EAACI, European Academy of Allergy and Clinical Immunology; EMT, epithelial-mesenchymal transition; EPOS, European Position Paper on Rhinosinusitis; EUFOREA, European Forum for Research and Education in Allergy and Airway Diseases; FeNO, fractional exhaled nitric oxide; GA^{2}LEN, Global Allergy and Asthma European Network; INCS, intra-nasal corticosteroid; LC-PUFA, long-chain polyunsaturated fatty acid; miRNA, microRNA.

asthma, and food allergy in 2016[1,2] and 2017.[3] EAACI published allergen-specific immunotherapy guidelines (AIT) in 2018,[4-18] and there have been extensive literature reviews and meta-analyses on the subject.[19-24]

Allergic diseases and asthma concern over 25% of the European population and cause a very high socio-economic burden. Strategies for early diagnosis, prevention, and control need to be anchored on a strong political agenda to implement the results of the research into practice. Two important political activities at the EU Parliament were reported in the journals: A European Summit on the Prevention and Self-Management of Chronic Respiratory Diseases (29 March 2017)[25] and a European Symposium on the awareness of allergy for a promotional campaign (26-28 April 2016).[26] This paper summarizes the 2018 achievements in asthma and rhinitis.

2 | GENETICS OF ALLERGIC DISEASES AND ASTHMA

The genetic predisposition to allergic diseases and asthma is well known and there is ongoing interest in determining how genetic variants affect disease susceptibility. A meta-analysis of 13 multiethnic studies from the Pharmacogenomics in Childhood Asthma indicated that rs7216389 polymorphism at the locus 17q21 is associated with a higher risk of exacerbations in asthmatic children, even when using oral corticosteroids.[27] Children carrying *interferon regulating factor* (*IRF-1*) polymorphisms, rs2706384, rs2070721, and rs10035166, resulted in the upregulation of pro-inflammatory genes and were at a higher risk of developing allergic asthma.[28]

Genetic mutations in the *SPINK5* gene, which encodes a serine peptidase inhibitor Kazal-type 5 essential for skin regeneration, were challenge-proven to be associated with IgE-mediated food allergy in children.[29] Preliminary results suggest that the polymorphism variant rs9325071 led to increased skin permeability as measured by transepidermal water loss. There is recent evidence suggesting that genetic variants related to adult lung function are associated with lung function and asthma in 10-year-old children.[30] Other factors also played a role, such as maternal atopy, tobacco smoke exposure, and birth weight.

3 | NOVEL HIGHLIGHTS ON MECHANISMS OF ALLERGIC DISEASE

Tumor necrosis factor–like weak inducer of apoptosis (TWEAK) is a transmembrane protein involved in many cellular processes, including airway inflammation. Sputum TWEAK expression is significantly higher in asthmatic children, and the levels can be directly correlated with asthma severity in children with noneosinophilic asthma.[31] Bronchial fibroblast-derived exosomes from severe asthmatic patients have a lower expression of transforming growth factor-beta 2 (TGF-β2), promoting epithelial cell proliferation.[32]

There are three distinct developmental stages of allergic rhinitis (AR), nonsensitized, asymptomatic sensitized, and allergen-induced symptomatic, with a different expression of Th2 cytokines at each stage.[33] Stimulation with Japanese cedar pollen (JCP) did not produce a response at the nonsensitized stage. The asymptomatic sensitized stage was characterized by production of IL-4 and a small amount of IL-13. The cells in the JCP-AR stage reacted to IL-33 and produced large amounts of IL-5 and IL13. In addition, ST2, an IL-33 receptor, is only upregulated in patients with allergen-induced AR and can be used as a marker for disease progression.

In a controlled allergen challenge facility, 3 hours of exposure to grass pollen led to DNA methylation changes in the peripheral blood mononuclear cells (PBMCs) of AR patients but not in healthy controls.[34] A lower *SLFN12* expression at baseline was associated with more severe allergic symptoms. These epigenetic changes can potentially be used as biomarkers of symptom severity. In a separate study, DNA methylation in chromosomal regions previously linked to asthma has been demonstrated to increase the risk of children with rhinovirus-induced wheezing to develop asthma.[35] In a 10-year follow-up study, local AR has been demonstrated to be an independent rhinitis phenotype with a low rate of conversion to systemic atopy but significantly worsening throughout the years.[36]

The epithelial barrier is the first line of defense against the external environment. A defective epithelial barrier has been associated with the development of AR with an increased histone deacetylase activity (HDAC).[37] The epithelial barrier function in allergic diseases is difficult to study in the intact lung and so epithelial cell lines are often used. However, care should be taken when analyzing the results as different cell lines exhibit different immune and epithelial barrier responses. In this context, Calu-3 cell lines and freshly isolated primary nasal epithelial cells had different responses to the exogenous stimuli *Staphylococcus aureus* enterotoxin B (SEB) and house dust mites (HDM).[38] The transmembrane protein cadherin-related family member 3 (CDHR3) was downregulated in peripheral blood leukocytes from children with rhinovirus-induced wheezing during the acute phase of bronchial obstruction but returned to healthy levels at the follow-up visit 2-3 months later, irrespective of the rhinovirus species.[39] It was proposed that the reduced *CDHR3* mRNA levels lead to an increase in the permeability of the airway epithelial barrier, increasing susceptibility to allergic diseases.

Chronic rhinosinusitis (CRS) is an inflammatory condition, commonly divided into CRS with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). Patients suffering from CRSsNP have significantly overexpressed leucine-rich repeat kinase 2 (LRRK2) and reduced NRON (noncoding repressor of NFAT) expression in nasal tissues compared with CRSwNP patients and healthy controls.[40] Pro-inflammatory cytokines modulate LRRK2 mRNA expression suggesting a negative role of LRRK2 during inflammation. Local IL-25 promotes the production of Th2 cytokines in polyp tissues of CRSwNP and may become of interest as a potential therapeutic target.[41] Myeloid dendritic cells (mDCs) present in nasal polyps have elevated surface expression of IL-17RB and ST2, suggesting that mDCs might be actively involved in IL-25- and IL-33-induced

Th2-type immune responses and eosinophilic inflammation.[42] The IL-25 receptor (IL-17RB) levels on eosinophil lineage–committed progenitor cells (EoP) are increased after exposure to allergen in allergic asthmatic patients. In addition, IL-25 promotes migration of EoP to the airways after allergen challenge.[43] These results were supported by the reduction of eosinophilic inflammation in the airways in IL-25 knockout mice sensitized to OVA.

B-cell responses after venom exposure are similar in both venom immunotherapy-treated allergic patients and naturally exposed healthy beekeepers, suggesting a similar role of regulatory B cells in allergen tolerance.[44] IL-10 is a key immune tolerance inducing cytokine that depicts Treg and Breg cells (Figure 1). The activation of protease-activated receptor (PAR)-2 on B cells inhibits IL-10 expression in peripheral B cells via upregulating Bcl2-like protein-12 (Bcl2L12).[45] Novel therapeutic candidates for the treatment of AR have been developed that compete with Bcl2L12 and restore IL-10 production, as recently demonstrated in a mouse model treated with Bcl2L12 shRNA liposomes (Figure 2).

Forkhead box protein-3 (Foxp3) is a key transcription factor of T regulatory (Treg) cells implicated in immune tolerance. A recent study in OVA-sensitized mice demonstrated that DCs overexpress Foxp3 when exposed to low doses of *Staphylococcal* enterotoxin B (SEB). These results suggest that SEB can be used as an adjuvant to enhance the specific immunotherapy (SIT) therapeutic efficiency.[46]

4 | PREDICTION AND PREVENTION OF ALLERGIC DISEASE

The sequential progression of eczema to hay fever and then asthma has been coined the atopic march. A systematic review of sibling and twin studies reveals that genetic factors are predominantly responsible for the progression of atopic march diseases while environmental factors only play a minor role.[47] There is ongoing interest in understanding the relationships between genetics, nutrition, and allergic diseases. Genetic variants in chromosome 17q21 are known to increase the risk of childhood asthma and it has been recently demonstrated that breastfeeding has a protective effect on these children, experiencing less respiratory symptoms.[48] Other early dietary factors, such as eating fish at least once a month at 12 months of age, reduced the risk of AR by age twelve.[49] Consumption of

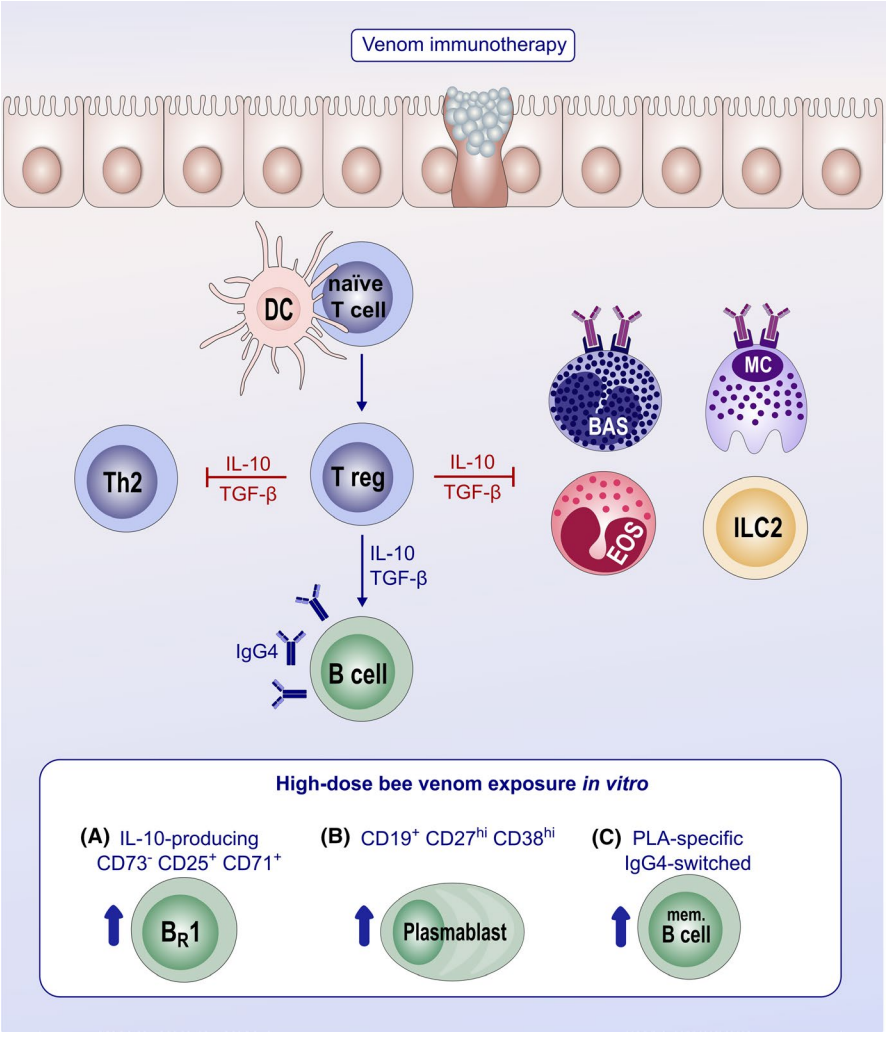

FIGURE 1 B-cell responses to venom immunotherapy. Venom immunotherapy induces the generation of regulatory T (T reg) cells, which produce IL-10 and TGF-β, and suppress the effector cells of allergic inflammation. In addition, these cytokines promote generation of IgG4 antibodies with the anti-inflammatory activity. High-dose bee venom exposure in vitro leads to an increase in the frequency of (A) IL-10-producing $CD73^{-}$ $CD25^{+}$ $CD71^{+}$ B cells, (B) $CD19^{+}$ $CD27^{hi}$ $CD38^{hi}$ and (c)PLA-specific IgG4-switched B cells

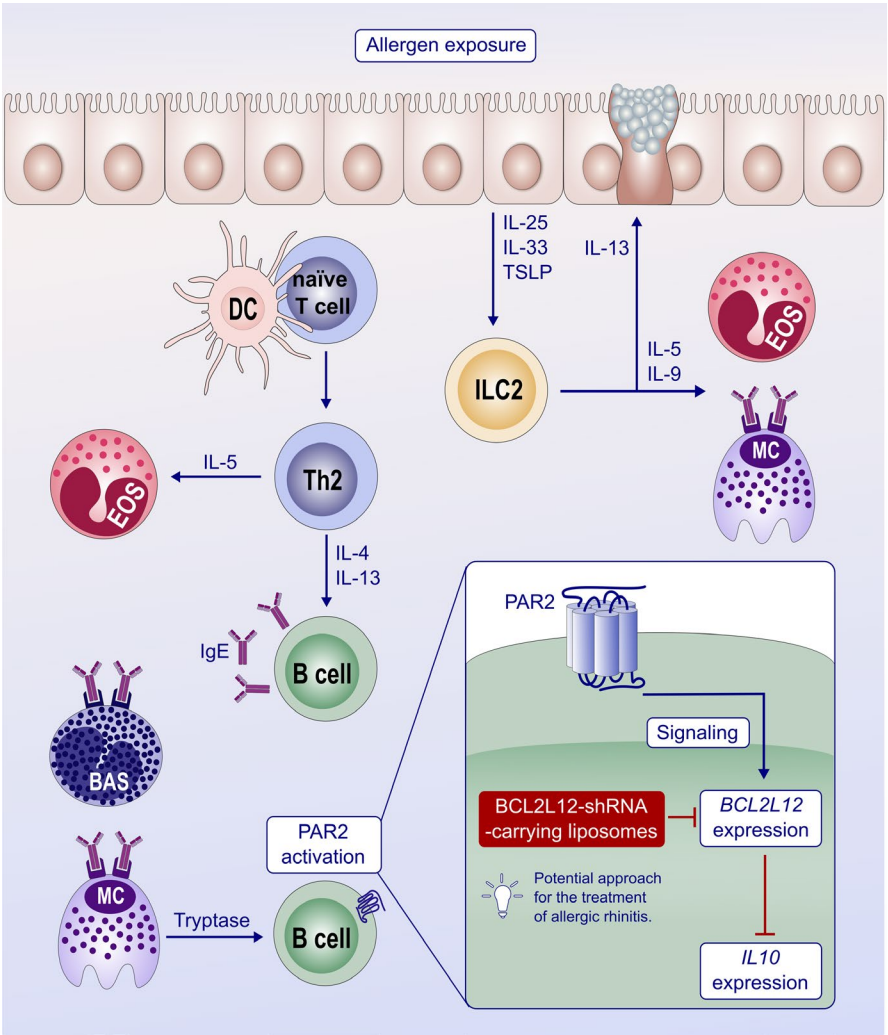

FIGURE 2 B-cell responses to allergen exposure. One of the pathological features of allergy is the compromised immunotolerance. An essential role in allergen tolerance is played by IL-10-producing B cells, whose function has been demonstrated to be impaired in allergic patients. Allergen exposure results in the activation of epithelial cells and secretion of epithelial-derived cytokines, such as IL-25, IL-33, and TSLP. These alarmins activate DCs, which present the antigen to naïve T cells, initiating Th2 cell differentiation, and induce type 2 cytokine release from ILCs. IL-13 released from ILC2s induces mucus secretion by goblet cells, whereas IL-5 and IL-9 recruit and activate mast cells and eosinophils. IL-4 primes B cells to synthesize IgE that binds to their receptors on basophils and mast cells. Mast cell–derived tryptase can activate a protease-activated receptor 2 (PAR2) on B cells. The activation of this receptor increases the expression of Bcl2L12 that has an inhibitory effect on IL-10. This effect can be reversed by treating B cells with Bcl2L12 shRNA-carrying liposomes

ultra-processed food and drink products in adolescents is associated with asthma and wheezing in a dose-dependent manner.[50]

There is increasing evidence linking vitamin D levels, the microbiome, and allergies.[51] Early-life probiotic supplementation with *Lactobacillus rhamnosus* HN001 reduces the incidence of eczema and hay fever at 11 years of age.[52] HN001 is not present in breastmilk and so direct infant supplementation is necessary to prevent infant eczema.[53] A systematic review and meta-analysis indicates that the intake of vitamin D during pregnancy, as measured from 25-hydroxyvitamin D levels, is associated with a reduction in the offspring's respiratory tract infections but there is no supporting evidence on a beneficial effect on asthma or allergies.[54] The airway microbiota composition in children is different in healthy, asthmatic, and remission groups.[55] The severity of bronchial hyperresponsiveness is associated with the presence of specific bacteria, upregulation of inflammatory genes, and lack of anti-inflammatory prostaglandin E2 genes in the airway microbiome of asthmatic children. A three-generational cohort study has recently shown that children whose maternal grandmother smoked during pregnancy are at higher risk of developing early persistent childhood asthma. These findings could be attributed to epigenetic alternations in the fetal germ cells.[56]

Wheezing preschool children have a characteristic metabolic urinary profile that can be used to predict if they will develop early-onset asthma after a 3-year follow-up.[57] Dimethylamine and allantoin are gut microbial-derived metabolites that have been associated with asthma development in early childhood and are potential prognostic markers of asthma.[58] A comprehensive systematic review and meta-analysis has recently reviewed bronchial hyperresponsiveness (BHR) in preterm-born subjects.[59] Bronchial provocation tests to methacholine and exercise indicated that preterm-born individuals had greater BHR compared with term-born, particularly those with chronic lung disease.

A data-driven analysis of the Canadian Asthma Primary Prevention Study has classified 525 children at high risk of asthma into three wheeze trajectory groups : low progressive (69%), early transient (10%), and early persistent (21%). These children were followed from birth to 15 years of age, considering both modifiable and nonmodifiable variables. Preventive measures targeting modifiable factors (smokers and pets in home, breastfeeding and daycare at 24 months) are most effective in the early persistent trajectory group.[60] In a group-based trajectory modeling analysis of 1,116 Japanese children, five phenotypes of asthma were identified according to their wheezing trajectories from 1 to 9 years of age.[61]

The original Asthma Predictive Index (API) was based on a parental questionnaire using a score from 1 to 5 (Likert scale) on the number of wheezing episodes within 1 year during the first 3 years. However, it does not specify the number of wheezing episodes required to be classified as frequent.[62] A recent retrospective cohort study suggests that 2 or more wheezing episodes within an interval of 3 years should be considered when applying API for retrospective studies using medical records.

5 | EPIDEMIOLOGY OF ALLERGIC DISEASE

Air monitoring of nonbiological components is routinely carried out by the government, unlike pollen and spore counts which are not always government-funded and freely accessible. Similarly to chemical pollutants, the current pollen and spore monitoring stations have now been mapped, facilitating the access of information.[63] The EAACI Task Force of the Immunotherapy and Aerobiology and Pollution Interest Group has defined pollen exposure times.[64] The suggested criteria have been computationally validated by analyzing Poaceae pollen count data from up to 40 pollen monitoring stations between 2012 and 2016.[65] There is a strong association between outdoor pollen levels and the number of asthma-related visits to the emergency department (ED) in children and adolescents aged <18 years, as recently demonstrated by a systematic review and meta-analysis.[66] Children aged between 5 and 17 years had the highest ED presentations from exposure to ambient grass pollen.

The impact of air pollution in asthma and rhinitis will be extensively studied in the new project POLLAR (Impact of air POLLution on Asthma and Rhinitis) of the European Institute of Innovation and Technology (EIT Health).[67] Air pollution in Taiwan is a major health concern. A nationwide study of a survey from 2011 with 6,346 children and a 2016-2017 survey with 11 585 children found an association between exposure to particulate matter ≤2.5 μm ($PM_{2.5}$) and childhood asthma. During this time period, there was a rise in the prevalence of asthma in spite of the 19% reduction in the concentration of $PM_{2.5}$ and a significant reduction in the effect of $PM_{2.5}$ on childhood asthma.[68]

In a Swedish birth cohort (BAMSE) study, it was found that exposure to mould or dampness during infancy was associated with the subsequent onset of asthma and rhinitis in adolescence (16 years old).[69] However, there was no correlation between IgE sensitization to aero- or food allergens and exposure to mould or dampness during infancy. In Brazil, asthmatic adults are commonly exposed to household air pollution (wood burning), cigarette smoke, or both. Among these factors, dual exposure led to the poorest asthma control and greatest asthma severity. In addition, indoor wood burning led to more detrimental respiratory problems compared to cigarette smoke.[70] Given the importance of airborne allergens in the home, a pilot study was undertaken to quantify the indoor concentration of allergens. The sample was collected using commercially available low volume air sampling pumps and DUSTREAT® dust samplers and quantified at a very low detection limit using a MARIA® immunoassay.[71] The effect of air conditioning and cold air on asthmatics has been recently reviewed.[72] The sudden change in temperature when entering an air-conditioned space can exacerbate the respiratory symptoms of patients with asthma and COPD.

Maternal hypothyroidism is known to increase the risk of childhood asthma in the offspring, especially if the mother did not receive thyroid hormone treatment during pregnancy.[73] The association between bronchial asthma and severe α-1-antitrypsin (AAT) deficiency is unclear. The proportion of individuals with deficient AAT genotypes is similar in asthmatic patients sensitized to HDM to that of the general Spanish population.[74]

It is well known that children growing up in farms have a reduced risk of developing asthma and allergic diseases. This protective "farm effect" was studied in farm children from different European countries in terms of living in close proximity to another farm using geocoded data from the GABRIELA study (2005-2007).[75] Clustered farms within a 100 m radius were exposed to a broader microbial diversity, additionally contributing to the protective farm effect of asthma. For the first time, the beneficial immunoregulatory effect of cattle farm dust was compared with the negative effect of urban PM using the same research methods, and so allowing for a systematic comparison between the two environments in vitro. The effects were measured by stimulating children's PMBCs with either farm dust extract or PM samples for 18 hours.[76]

Fractional exhaled nitric oxide (FeNO) levels and sputum eosinophil counts can be used as complementary diagnostic tools for occupational asthma. This is particularly valuable for subjects who fail to demonstrate nonspecific bronchial hyperresponsiveness as measurements are often taken outside the workplace, some time after exposure to the sensitizing agent.[77] A manufacturing and packaging factory worker has been recently reported with occupational asthma from exposure to *Gammarus* shrimp powder due to sensitization to the Pen m 4 allergen.[78]

6 | PREVALENCE OF ALLERGIC RHINITIS

Allergic rhinitis is a global health concern affecting more than 400 million people worldwide. The Allergy Management Support System (AMSS) was established to support general practitioners in the management of allergy patients in primary care.[79] A recent study evaluated the usefulness and compliance of the AMSS recommendations which are sent to the general practitioner within 10 working days after receiving the sIgE test results. The majority of General Practitioners (GPs) who responded to the AMSS questionnaire gave positive feedback suggesting that AMSS can be used to support the management of allergic patients in primary care. The Allergic Rhinitis Clinical Investigator Collaborative (AR-CIC) is a network of experienced AR specialists that are continuously working on improving research tools to analyze data obtained from nasal allergen challenge tests. The network validated the efficacy of the current AR-CIC

nasal allergen challenge procedure of a novel peptide-based immunotherapy for cat allergy.[80]

House dust mites are one of the major sources of indoor allergens in Central Europe, and cockroach allergy has been associated with the onset of asthma in the United States and Asia. In a study of the sensitization profiles of HDM and cockroach allergic patients living in Central Europe, it was found that most patients were sensitized to more than one allergen component from the same source.[81] The authors suggested quantifying at least the three major mite components Der f 1, Der p 1, and Der f 2. A meta-analysis and systematic literature review has recently reported on the prevalence of spider mite sensitivity.[82] Even though there was a high heterogeneity and publication bias, the study indicated a 22.9% global prevalence of allergies to spider mites with a 7% monosensitization rate, suggesting that spider mites produce unique allergens.

The symptoms caused by AR can have a significant impairment on quality of life (QoL) but little is known on the QoL of NAR patients even though there are estimates of 200-400 million people suffering from this condition. In contrast to the well-known significant impairment of QoL in AR patients, the degree of impairment in QoL in NAR remained unknown for a long time due to a lack of a validated questionnaire to assess QoL in the NAR patient group. A significant QoL impairment was found in both AR and NAR patients combined with a low treatment satisfaction, emphasizing the need for adequate treatment, especially in the NAR patient group.[83] US swimmers have a higher prevalence of rhinitis than the general population. A questionnaire-based study assessed the prevalence of rhinitis in elite and nonelite swimmers, other athletes, and the general population, focusing on the swimming performance and QoL of the participants.[84] These findings indicate a higher prevalence of NAR in swimmers compared to controls, but not of AR compared to controls, highlighting the need for appropriate management of rhinitis in swimming athletes.

7 | MULTIMORBIDITY

Allergic rhinitis and nonallergic rhinitis (NAR) are associated with poorer asthma control. The BAMSE birth cohort study showed peripheral airway obstruction in individuals with allergic asthma with or without rhinitis, as measured by impulse oscillometry.[85] These subjects also had significantly elevated levels of FeNO and blood eosinophils compared with nonallergic asthmatic individuals. These findings suggest that small airway disease can be attributed to the eosinophilic inflammation in allergic asthma.

The relationship between lung function and multimorbidity of asthma and rhinitis was studied in the Multicenter Allergy Study (MAS) birth cohort at different time points up to adolescence.[86] Single and multimorbid phenotypes could not be distinguished based on lung function data alone. However, bronchial provocation tests clearly identified individuals with asthma and/or rhinitis. The severity of bronchial hyperresponsiveness was associated with multimorbidity, particularly when the children reached 20 years of age. A separate study with participants from the French EGEA and Swedish BAMSE indicated that multimorbid asthma and rhinitis continue from adolescence to adulthood.[87] The four asthma-rhinitis phenotypes had different IgE sensitization patterns against the 64 aeroallergens measured using the MEDALL-chip microarray. There were also differences between the two populations (EGEA and BAMSE) due to the different allergenic environments and asthma phenotypes considered.

A 15-year Finnish follow-up of a population-based cohort revealed higher mortality of adults with asthma.[88] Increased mortality was attributed to the development of COPD, malignant respiratory tract neoplasms, and cardiovascular diseases. Smoking is one of the major factors contributing to total mortality. In the studied population, asthmatics with AR and/or allergic conjunctivitis have a reduced risk of mortality.

8 | DIAGNOSIS OF CHRONIC RHINOSINUSITIS

The recommended approach to clinical diagnosis of CRS has been outlined by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS).[89] It has been defined as experiencing cardinal sinonasal symptoms for at least 3 months, in addition to objective evidence obtained from endoscopic examination and/or CT scan. However, the EPOS guidelines do not specify how to measure the severity or frequency of subjective patient symptoms. Exploratory factor analysis (EFA) has been recently applied to a longitudinal study with 3,535 participants responding to a questionnaire at different time points over 16 months.[90] Five symptom factors have been clustered by analyzing the EFA data on symptom frequency, severity, and degree of discomfort.

Chronic rhinosinusitis is a heterogeneous disease with different clinical phenotypes that are not fully understood. Seven different endotypes have been identified in 246 postoperative Chinese CRS patients by integrating cellular, molecular, and clinical variables in the same cluster analysis, providing insights into the underlying pathological mechanisms.[91] This cluster analysis revealed a new endotype of CRS characterized by upregulation of IL-10 and difficult-to-treat CRS.

The Sino-Nasal Outcome Test (SNOT)-22 is a widely used, validated questionnaire. The SNOT-22 scores correlate with the visual analogue scale (VAS) for total nasal symptom score and individual sinonasal symptoms.[92] In addition, the SNOT-22 scores had a strong correlation with both chronic rhinitis phenotypes (CRSwNP, CRSsNP) but varied with different levels of disease control. These results suggest that VAS can be used as a simple tool to measure CRS disease severity and support the use of VAS in mHealth apps.

Allergic rhinitis can severely impact QoL and sleep, which can lead to anxiety and depression. In a large Spanish cohort, the quality of life, anxiety, depression, and quality of sleep were evaluated in patients with perennial and seasonal AR rhinitis, in and out of the

pollen season. Using validated questionnaires, symptom severity was directly correlated with worsening of all the variables measured, regardless of the duration of allergen exposure.[93]

9 | ASTHMA TREATMENT

Daily inhaled corticosteroids are the most commonly used treatment for mild persistent asthma. There is ongoing research into alternative methods, such as the intermittent administration of beclomethasone in children.[94] Tiotropium has been recently demonstrated to be a safe add-on therapy of inhaled corticosteroids in children aged 6-11 with symptomatic moderate asthma and its pharmacokinetic parameters were similar to those obtained in adolescents and adults.[95]

After mites and pollens, animals are the third leading cause of allergic asthma. The recommendations for the diagnosis and treatment of dog and cat allergies have been recently reviewed in a consensus document prepared using the RAND/UCLA Appropriateness Method.[96]

Severe asthma that is nonresponsive to inhaled corticosteroids represents a significant socio-economic burden. Children with severe asthma that is nonresponsive to standard inhaled corticosteroids have a distinct pattern of transcription factors expressed in CD4 T cells compared with nonsevere asthma.[97] The clinical data from the Italian Registry (RItA) from 493 severe/uncontrolled asthmatic patients across 27 clinical centres were analyzed and found to be similar to those obtained from other European and US studies.[98] In a real-life study, a large cohort of Japanese patients with severe or life-threatening asthma were clustered into three groups according to the visual analogue scale scores obtained starting from 14 days prior to hospitalization, in order to identify patterns leading to severe or life-threatening exacerbations.[99] The findings highlight the need for personalized asthma management, and various asthma treatment options for patients in each cluster have been proposed.

Montelukast is a cysteinyl-leukotriene-1 receptor antagonist and has been recently studied as a drug candidate for reducing the number of wheezing episodes in children 3-36 months of age.[100] The randomized, double-blinded, placebo-controlled study suggested that treatment with montelukast had beneficial effects only during the first 7 days of treatment compared to placebo and may be used to replace salbutamol during that time period.

IgE is a promising therapeutic target for the treatment of allergic diseases, including allergic severe asthma, and to date, omalizumab is the only FDA-approved recombinant humanized anti-IgE antibody. Novel research on IgE-targeted therapies has been recently reviewed focusing on serum IgE neutralization, inhibiting IgE receptors in effector cells, and targeting IgE^+ plasma cells.[101] Baseline blood eosinophil levels can be used as prognostic markers for response to omalizumab in patients with allergic asthma.[102] A higher eosinophil count corresponded to a more effective omalizumab response as observed from an increased rate of reduction in asthma exacerbations.

Allied health professional (AHP) training in asthma and allergic diseases varies considerably between different countries and professions. Allergic diseases are complex and warrant an interdisciplinary team of professionals including nurses, dieticians, psychologists, pharmacists, etc. In order to ensure standardized and qualified knowledge, EAACI has assembled a Task Force that has set guidelines for the diagnosis and management of allergic diseases.[103] The diagnostic therapeutic educational pathway (DTEP) is an educational programme on asthma prevention, symptoms, and treatment. The impact of this course was assessed in children and adolescents before and after attending DTEP.[104] There was a significant improvement in almost all health outcomes measured after attending the DTEP course across both age-groups and particularly in the reduction of the rate of drug prescriptions.

10 | TREATMENT OF ALLERGIC RHINITIS

There is a large discrepancy between what physicians instruct to AR patients and what they do in practice. The need for personalized medicine with a good fit for the patient's demands was discussed during a EUFOREA symposium at the 2017 European Rhinology Research Forum held in Brussels, Belgium.[105] Data collected from the Mobile Airways Sentinel networK (MASK) app, named MASK-air (formerly the *Allergy Diary*, indicate that there is poor patient compliance and that they prefer to self-medicate.[106] Nasal sprays provide the rapid onset of action demanded by patients. MP-AzeFlu is a nasal spray with a novel azelastine (AZE) and fluticasone propionate (FP) formulation. It has a 5-minute onset of action threshold and in 15 minutes provides clinically relevant symptom relief. The AZE-FP (MP29-02) formulation reduced nasal hyperreactivity and nasal inflammatory mediators in patients with HDM-AR.[107] There is substantial clinical evidence on the efficacy of capsaicin nasal spray for the treatment of idiopathic rhinitis (IR). However, up to half of IR patients have had to be excluded from clinical trials so far because they did not meet strict inclusion criteria. The capsaicin clinical response in these mixed rhinitis patients was confirmed after 12 weeks of treatment.[108] The presence of NHR in both groups was a good indicator of therapeutic responsiveness.

11 | TREATMENT OF CHRONIC RHINOSINUSITIS

Glucocorticoids are commonly prescribed to reduce the inflammation of CRS, albeit with varied success. An olfactory cleft score of 3.5, as measured from a CT scan, is a prognostic indicator of a positive therapeutic response to glucocorticoid therapy in CRSwNP patients with similar accuracy as blood eosinophil counts.[109]

12 | ALLERGEN IMMUNOTHERAPY (AIT)

Several important papers on AIT have been recently published. Recent studies confirmed AIT with grass allergen peptides (170 μg

over 3 weeks)[110,111] and depigmented polymerized allergen extracts[112] as safe and effective treatments for local AR caused by grass pollen sensitization. A maximum cumulative dose of 490 μg of the grass pollen peptides was well tolerated with only a few minor adverse reactions.[113] After completing AIT, symptoms can reoccur within a few years but can be prevented by receiving a short course booster. This has been demonstrated with recurrent pollen-induced seasonal AR patients that experienced a reduction of symptoms when administered with an ultra-short-course booster AIT using tyrosine-absorbed allergoids containing the adjuvant monophosphoryl lipid A (MPL((R)).[114] During the first year of birch pollen AIT, inhibition mediator release assays using the patient's own IgE indicated that the clinical outcome depends on the AIT-induced IgG antibodies to develop novel epitope specificities that can inhibit IgE binding to Bet v 1.[115]

Sublingual immunotherapy (SLIT) is a particularly attractive alternative to AIT due to its ease of administration. The clinical efficacy and positive safety profile of the SQ HDM SLIT-tablets in patients older than 12 years are known and have been recently extended to include children (5-11 years) with moderate-to-severe SQ HDM AR[116] and with perennial AR.[117] The conjunctival provocation test is a good predictor of SLIT outcome after only 4 weeks of treatment and can be used to identify candidates that will benefit from SLIT for an upcoming pollen season.[118] The levels of HDM-reactive T-cell subsets, $ST2^{+}CD45RO^{+}CD4^{+}$ and $IL\text{-}5^{+}IL\text{-}13^{+}CD27^{-}CD161^{+}CD4^{+}$, from PBMCs are reduced after 1 year of HDM SLIT and may be used as biomarkers of a positive therapeutic outcome.[119] These cells have been proposed to play a role in the development of AR as pathogenic memory Th2 cells.

A novel subcutaneous AIT formulation (gpASIT + ^{TM}) containing Lolium perenne peptides (LPP) and with a short up-dosing phase has been developed to treat grass pollen-induced seasonal ARC. Three-week immunotherapy with 170 μg LPP reduced CPT reactivity significantly and increased protective specific antibodies. Grass and olive pollen seasons in Spain overlap and so it is difficult to identify the true nature of the allergen in patients with

TABLE 1 List of EAACI Guidelines and Position Papers and Editorials related to them published in 2018

Title	References
EAACI guidelines on allergen immunotherapy – Out with the old and in with the new	4
Allergen manufacturing and quality aspects for allergen immunotherapy in Europe and the United States: An analysis from the EAACI AIT Guidelines Project	5
The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update	8
Allergen immunotherapy in people, dogs, cats and horses – differences, similarities and research needs	9
EAACI guidelines on allergen immunotherapy: Executive statement	10
EAACI guidelines on allergen immunotherapy: IgE-mediated food allergy	11
EAACI guidelines on allergen immunotherapy: Allergic rhinoconjunctivitis	15
Challenges in the implementation of the EAACI AIT guidelines: A situational analysis of current provision of allergen immunotherapy	16
Influenza burden, prevention, and treatment in asthma-A scoping review by the EAACI Influenza in asthma task force	17
EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy	18
Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: An EAACI position paper	123
Promoting and achieving excellence in the delivery of Integrated Allergy Care: the European Academy of Allergy & Clinical Immunology competencies for allied health professionals working in allergy	103
The urgent need for a harmonized severity scoring system for acute allergic reactions	127
Current practice of allergy diagnosis and the potential impact of regulation in Europe	128
EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents	129
Emerging roles of innate lymphoid cells in inflammatory diseases: Clinical implications	130
The roadmap for allergology in Europe: The subspecialty of allergology as “stop-over” on the way to a full specialty. An EAACI position statement	131
AllergoOncology: Opposite outcomes of immune tolerance in allergy and cancer	132
EAACI position paper on how to classify cutaneous manifestation of drug hypersensitivity	133
An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity	134
Drug hypersensitivity in children: Report from the pediatric task force of the EAACI Drug Allergy Interest Group	135
The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria	136
EAACI Position paper on the standardization of nasal allergen challenges	137

seasonal AR. The molecular sensitization pattern revealed that most patients (76.2%) in a Spanish paediatric population were sensitized to both major grass (Phl p 1 + 5) and olive (Ole e 1) pollen allergens.[120]

Very preterm-born children are predisposed to respiratory diseases due to improper lung maturation. Protein supplementation of preterm formula and maternal milk improves lung function at 6 years of age.[121] Farming mothers have a higher exposure to endotoxins resulting in functional changes in the neonatal TLR2 gene polymorphism that modulates the TLR2-Treg-Th axis, leading to a protective effect against allergy in the offspring.[122] There is an ongoing search for biomarkers of disease and for predicting AIT clinical outcome. The EAACI Task Force on "Biomarkers for monitoring the clinical efficacy of allergen immunotherapy" has recently published a comprehensive literature review on the biomarkers currently used for predicting the AIT clinical outcome in allergic rhinoconjunctivitis (ARC) patients with and without asthma.[123]

13 | SOCIO-ECONOMIC IMPACT

A Swedish population-based birth cohort study (BAMSE) investigated how asthma affects school performance in adolescents.[124] Multimorbidity and poor asthma control increased the likelihood of poorer school performance. Allergic rhinitis lowers the QoL and can lead to loss of productivity in the workplace. On average, AR patients are absent 1.5 days from work or school over a 3-month period. A recent study indicates that the severity of depressed mood is a more important factor than nasal symptoms in determining the loss of productivity caused by AR.[125]

In a previous systematic review (1990-2012),[126] nonpharmacological asthma interventions, such as asthma management, education, and environmental interventions, were reported as cost-effective. However, methods used to estimate costs and outcomes were not thoroughly studied. An updated systematic review (1990-2016) has been recently published that highlights the strong variability in methods used to estimate costs and outcomes. The bottom-up approach was the most frequently used method to estimate resource-use costs and the clinical outcomes were most often measured using a self-report asthma questionnaire, mainly the Asthma Quality of Life Questionnaire (AQLQ) and the EuroQol-5 Dimensions (EQ-5D). The list of guidelines and Position papers published by EAACI is given in Table 1.

CONFLICTS OF INTEREST

Dr Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, outside the submitted work. Dr Akdis reports grants from Allergopharma, grants from Idorsia, grants from Swiss National Science Foundation, grants from Christine Kühne-Center for Allergy Research and Education, grants from European Commission's Horison's 2020 Framework Programme, Cure, other from Sanofi-Aventis_Regeneron, grants from Novartis Research Institutes, grants from Astra Zeneca, grants from Scibase, outside the submitted work. Dr Grattan reports Co-Editor in Chief Clinical and Translational Allergy. Dr Jutel reports personal fees from ALK-Abello, personal fees from Allergopharma, personal fees from Stallergenes, personal fees from Anergis, personal fees from Allergy Therapeutics, personal fees from Circassia, personal fees from Leti, personal fees from Biomay, personal fees from HAL, during the conduct of the study; personal fees from Astra-Zeneka, personal fees from GSK, personal fees from Novartis, personal fees from Teva, personal fees from Vectura, personal fees from UCB, personal fees from Takeda, personal fees from Roche, personal fees from Janssen, personal fees from Medimmune, personal fees from Chiesi, outside the submitted work. The remaining authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Each author reviewed the referenced papers and the text. The paper was written by JB. All authors read and approved the final manuscript.

ORCID

Cezmi A. Akdis https://orcid.org/0000-0001-8020-019X

Ioana Agache https://orcid.org/0000-0001-7994-364X

REFERENCES

1. Bousquet J, Grattan C, Bieber T, et al. Prediction and prevention of allergy and asthma in EAACI journals (2016). *Clin Transl Allergy*. 2017;7:46.
2. Wahn U, Matricardi PM, Bieber T, et al. Food allergy in EAACI journals (2016). *Pediatr Allergy Immunol*. 2017;28(8):825-830.
3. Bousquet J, Akdis CA, Grattan C, et al. Highlights and recent developments in airway diseases in EAACI journals (2017). *Clin Transl Allergy*. 2018;8:49.
4. Agache I. EAACI guidelines on allergen immunotherapy-out with the old and in with the new. *Allergy*. 2018;73(4):737-738.
5. Bonertz A, Roberts G, Slater JE, et al. Allergen manufacturing and quality aspects for allergen immunotherapy in Europe and the United States: an analysis from the EAACI AIT Guidelines Project. *Allergy*. 2018;73(4):816-826.
6. Bonertz A, Roberts GC, Hoefnagel M, et al. Challenges in the implementation of EAACI guidelines on allergen immunotherapy: a global perspective on the regulation of allergen products. *Allergy*. 2018;73(1):64-76.
7. Larenas-Linnemann D, Antolin-Amerigo D, Parisi C, et al. National clinical practice guidelines for allergen immunotherapy: an international assessment applying AGREE-II. *Allergy*. 2018;73(3):664-672.
8. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2017 revision and update. *Allergy*. 2018;73(8):1575-1596.
9. Mueller RS, Jensen-Jarolim E, Roth-Walter F, et al. Allergen immunotherapy in people, dogs, cats and horses – differences, similarities and research needs. *Allergy*. 2018;73(10):1989-1999.
10. Muraro A, Roberts G, Halken S, et al. EAACI guidelines on allergen immunotherapy: executive statement. *Allergy*. 2018;73(4):739-743.

11. Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2018;73(4):799-815.
12. Pfaar O, Bonini S, Cardona V, et al. Perspectives in allergen immunotherapy: 2017 and beyond. *Allergy*. 2018;73(Suppl 104):5-23.
13. Pfaar O, Lou H, Zhang Y, Klimek L, Zhang L. Recent developments and highlights in allergen immunotherapy. *Allergy*. 2018;73(12):2274-2289.
14. Reitsma S, Subramaniam S, Fokkens W, Wang Y. Recent developments and highlights in rhinitis and allergen immunotherapy. *Allergy*. 2018;73(12):2306-2313.
15. Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: allergic rhinoconjunctivitis. *Allergy*. 2018;73(4):765-798.
16. Ryan D, Gerth van Wijk R, Angier E, et al. Challenges in the implementation of the EAACI AIT guidelines: a situational analysis of current provision of allergen immunotherapy. *Allergy*. 2018;73(4):827-836.
17. Schwarze J, Openshaw P, Jha A, et al. Influenza burden, prevention, and treatment in asthma-A scoping review by the EAACI Influenza in asthma task force. *Allergy*. 2018;73(6):1151-1181.
18. Sturm GJ, Varga EM, Roberts G, et al. EAACI guidelines on allergen immunotherapy: hymenoptera venom allergy. *Allergy*. 2018;73(4):744-764.
19. Asaria M, Dhami S, van Ree R, et al. Health economic analysis of allergen immunotherapy for the management of allergic rhinitis, asthma, food allergy and venom allergy: a systematic overview. *Allergy*. 2018;73(2):269-283.
20. Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy*. 2017;72(12):1825-1848.
21. Dhami S, Nurmatov U, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. *Allergy*. 2017;72(11):1597-1631.
22. Dhami S, Zaman H, Varga EM, et al. Allergen immunotherapy for insect venom allergy: a systematic review and meta-analysis. *Allergy*. 2017;72(3):342-365.
23. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Macchia L, Di Lorenzo G. Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review. *Allergy*. 2017;72(5):691-704.
24. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy*. 2017;72(8):1133-1147.
25. Hellings PW, Borrelli D, Pietikainen S, et al. European summit on the prevention and self-management of chronic respiratory diseases: report of the European Union Parliament Summit (29 March 2017). *Clin Transl Allergy*. 2017;7:49.
26. Muraro A, Steelant B, Pietikainen S, et al. European symposium on the awareness of allergy: report of the promotional campaign in the European Parliament (26–28 April 2016). *Allergy*. 2017;72(2):173-176.
27. Farzan N, Vijverberg SJ, Hernandez-Pacheco N, et al. 17q21 variant increases the risk of exacerbations in asthmatic children despite inhaled corticosteroids use. *Allergy*. 2018;73(10):2083-2088.
28. Landgraf-Rauf K, Boeck A, Siemens D, et al. IRF-1 SNPs influence the risk for childhood allergic asthma: a critical role for pro-inflammatory immune regulation. *Pediatr Allergy Immunol*. 2018;29(1):34-41.
29. Ashley SE, Tan HT, Vuillermin P, et al. The skin barrier function gene SPINK5 is associated with challenge-proven IgE-mediated food allergy in infants. *Allergy*. 2017;72(9):1356-1364.
30. Shagiwal SS, den Dekker HT, de Jongste JC, et al. Influence of genetic variants on childhood lung function – the Generation R Study. *Pediatr Allergy Immunol*. 2018;29(6):589-595.
31. Kim SY, Kim JD, Sol IS, et al. Sputum TWEAK expression correlates with severity and degree of control in non-eosinophilic childhood asthma. *Pediatr Allergy Immunol*. 2018;29(1):42-49.
32. Haj-Salem I, Plante S, Gounni AS, Rouabhia M, Chakir J. Fibroblast-derived exosomes promote epithelial cell proliferation through TGF-beta2 signalling pathway in severe asthma. *Allergy*. 2018;73(1):178-186.
33. Iinuma T, Okamoto Y, Morimoto Y, et al. Pathogenicity of memory Th2 cells is linked to stage of allergic rhinitis. *Allergy*. 2018;73(2):479-489.
34. North ML, Jones MJ, MacIsaac JL, et al. Blood and nasal epigenetics correlate with allergic rhinitis symptom development in the environmental exposure unit. *Allergy*. 2018;73(1):196-205.
35. Lund RJ, Osmala M, Malonzo M, et al. Atopic asthma after rhinovirus-induced wheezing is associated with DNA methylation change in the SMAD3 gene promoter. *Allergy*. 2018;73(8):1735-1740.
36. Rondon C, Campo P, Eguiluz-Gracia I, et al. Local allergic rhinitis is an independent rhinitis phenotype: the results of a 10-year follow-up study. *Allergy*. 2018;73(2):470-478.
37. Steelant B, Wawrzyniak P, Martens K, et al. Blocking histone deacetylase activity as a novel target for epithelial barrier defects in patients with allergic rhinitis. *J Allergy Clin Immunol*. pii: S0091-6749(19)30615-3.
38. Martens K, Hellings PW, Steelant B. Calu-3 epithelial cells exhibit different immune and epithelial barrier responses from freshly isolated primary nasal epithelial cells in vitro. *Clin Transl Allergy*. 2018;8:40.
39. Stenberg Hammar K, Niespodziana K, van Hage M, et al. Reduced CDHR3 expression in children wheezing with rhinovirus. *Pediatr Allergy Immunol*. 2018;29(2):200-206.
40. Ma Y, Zheng C, Shi L. The kinase LRRK2 is differently expressed in chronic rhinosinusitis with and without nasal polyps. *Clin Transl Allergy*. 2018;8(1):8.
41. Hong HY, Chen FH, Sun YQ, et al. Local IL-25 contributes to Th2-biased inflammatory profiles in nasal polyps. *Allergy*. 2018;73(2):459-469.
42. Zheng R, Wang D, Wang K, et al. Elevated expression of IL-17RB and ST2 on myeloid dendritic cells is associated with a Th2-skewed eosinophilic inflammation in nasal polyps. *Clin Transl Allergy*. 2018;8:50.
43. Tang W, Smith SG, Du W, et al. Interleukin-25 and eosinophils progenitor cell mobilization in allergic asthma. *Clin Transl Allergy*. 2018;8:5.
44. Boonpiyathad T, Meyer N, Moniuszko M, et al. High-dose bee venom exposure induces similar tolerogenic B-cell responses in allergic patients and healthy beekeepers. *Allergy*. 2017;72(3):407-415.
45. Xue JM, Yang LT, Yang G, et al. Protease-activated receptor-2 suppresses interleukin (IL)-10 expression in B cells via up-regulating Bcl2L12 in patients with allergic rhinitis. *Allergy*. 2017;72(11):1704-1712.
46. Liu XY, Xu LZ, Luo XQ, et al. Forkhead box protein-3 (Foxp3)-producing dendritic cells suppress allergic response. *Allergy*. 2017;72(6):908-917.
47. Khan SJ, Dharmage SC, Matheson MC, Gurrin LC. Is the atopic march related to confounding by genetics and early-life environment? A systematic review of sibship and twin data. *Allergy*. 2018;73(1):17-28.
48. Gorlanova O, Illi S, Toncheva AA, et al. Protective effects of breastfeeding on respiratory symptoms in infants with 17q21 asthma risk variants. *Allergy*. 2018;73(12):2388-2392.
49. Vasileiadou S, Wennergren G, Stromberg Celind F, et al. Eating fish and farm life reduce allergic rhinitis at the age of twelve. *Pediatr Allergy Immunol*. 2018;29(3):283-289.

50. Melo B, Rezende L, Machado P, Gouveia N, Levy R. Associations of ultra-processed food and drink products with asthma and wheezing among Brazilian adolescents. *Pediatr Allergy Immunol*. 2018;29(5):504-511.
51. Wjst M. Linking vitamin D, the microbiome and allergy. *Allergy*. 2017;72(3):329-330.
52. Wickens K, Barthow C, Mitchell EA, et al. Effects of Lactobacillus rhamnosus HN001 in early life on the cumulative prevalence of allergic disease to 11 years. *Pediatr Allergy Immunol*. 2018;29(8):808-814.
53. Wickens K, Barthow C, Mitchell EA, et al. Maternal supplementation alone with Lactobacillus rhamnosus HN001 during pregnancy and breastfeeding does not reduce infant eczema. *Pediatr Allergy Immunol*. 2018;29(3):296-302.
54. Pacheco-Gonzalez RM, Garcia-Marcos L, Morales E. Prenatal vitamin D status and respiratory and allergic outcomes in childhood: a meta-analysis of observational studies. *Pediatr Allergy Immunol*. 2018;29(3):243-253.
55. Kim BS, Lee E, Lee MJ, et al. Different functional genes of upper airway microbiome associated with natural course of childhood asthma. *Allergy*. 2018;73(3):644-652.
56. Braback L, Lodge CJ, Lowe AJ, Dharmage SC, Olsson D, Forsberg B. Childhood asthma and smoking exposures before conception-A three-generational cohort study. *Pediatr Allergy Immunol*. 2018;29(4):361-368.
57. Carraro S, Bozzetto S, Giordano G, et al. Wheezing preschool children with early-onset asthma reveal a specific metabolomic profile. *Pediatr Allergy Immunol*. 2018;29(4):375-382.
58. Chiu CY, Lin G, Cheng ML, et al. Longitudinal urinary metabolomic profiling reveals metabolites for asthma development in early childhood. *Pediatr Allergy Immunol*. 2018;29(5):496-503.
59. Kotecha S, Clemm H, Halvorsen T, Kotecha SJ. Bronchial hyper-responsiveness in preterm-born subjects: a systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2018;29(7):715-725.
60. Owora AH, Becker AB, Chan-Yeung M, et al. Wheeze trajectories are modifiable through early-life intervention and predict asthma in adolescence. *Pediatr Allergy Immunol*. 2018;29(6):612-621.
61. Yang L, Narita M, Yamamoto-Hanada K, Sakamoto N, Saito H, Ohya Y. Phenotypes of childhood wheeze in Japanese children: a group-based trajectory analysis. *Pediatr Allergy Immunol*. 2018;29(6):606-611.
62. Wi CI, Krusemark EA, Voge G, et al. Usefulness of asthma predictive index in ascertaining asthma status of children using medical records: an explorative study. *Allergy*. 2018;73(6):1276-1283.
63. Buters J, Antunes C, Galveias A, et al. Pollen and spore monitoring in the world. *Clin Transl Allergy*. 2018;8:9.
64. Pfaar O, Bastl K, Berger U, et al. Defining pollen exposure times for clinical trials of allergen immunotherapy for pollen-induced rhinoconjunctivitis – an EAACI position paper. *Allergy*. 2017;72(5):713-722.
65. Karatzas K, Riga M, Berger U, Werchan M, Pfaar O, Bergmann KC. Computational validation of the recently proposed pollen season definition criteria. *Allergy*. 2018;73(1):5-7.
66. Erbas B, Jazayeri M, Lambert KA, et al. Outdoor pollen is a trigger of child and adolescent asthma emergency department presentations: a systematic review and meta-analysis. *Allergy*. 2018;73(8):1632-1641.
67. Bousquet J, Anto JM, Annesi-Maesano I, et al. POLLAR: impact of air POLLution on Asthma and Rhinitis; a European Institute of Innovation and Technology Health (EIT Health) project. *Clin Transl Allergy*. 2018;8:36.
68. Chen BY, Chen CH, Chuang YC, Wu YH, Pan SC, Guo YL. Changes in the relationship between childhood asthma and ambient air pollution in Taiwan: results from a nationwide survey repeated 5 years apart. *Pediatr Allergy Immunol*. 2019;30(2):188-194.
69. Thacher JD, Gruzieva O, Pershagen G, et al. Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort. *Allergy*. 2017;72(6):967-974.
70. Fernandes A, de Souza-Machado C, Pinheiro GP, et al. Dual exposure to smoking and household air pollution is associated with an increased risk of severe asthma in adults in Brazil. *Clin Transl Allergy*. 2018;8:48.
71. Tulum L, Deag Z, Brown M, et al. Airborne protein concentration: a key metric for type 1 allergy risk assessment-in home measurement challenges and considerations. *Clin Transl Allergy*. 2018;8:10.
72. D'Amato M, Molino A, Calabrese G, Cecchi L, Annesi-Maesano I, D'Amato G. The impact of cold on the respiratory tract and its consequences to respiratory health. *Clin Transl Allergy*. 2018;8:20.
73. Liu X, Andersen SL, Olsen J, et al. Maternal hypothyroidism in the perinatal period and childhood asthma in the offspring. *Allergy*. 2018;73(4):932-939.
74. Suarez-Lorenzo I, de Castro FR, Cruz-Niesvaara D, Herrera-Ramos E, Rodriguez-Gallego C, Carrillo-Diaz T. Alpha 1 antitrypsin distribution in an allergic asthmatic population sensitized to house dust mites. *Clin Transl Allergy*. 2018;8:44.
75. Muller-Rompa S, Markevych I, Hose AJ, et al. An approach to the asthma-protective farm effect by geocoding: good farms and better farms. *Pediatr Allergy Immunol*. 2018;29(3):275-282.
76. Martikainen MV, Ronkko TJ, Schaub B, et al. Integrating farm and air pollution studies in search for immunoregulatory mechanisms operating in protective and high-risk environments. *Pediatr Allergy Immunol*. 2018;29(8):815-822.
77. Beretta C, Rifflart C, Evrard G, Jamart J, Thimpont J, Vandenplas O. Assessment of eosinophilic airway inflammation as a contribution to the diagnosis of occupational asthma. *Allergy*. 2018;73(1):206-213.
78. Sogo A, Cruz MJ, Amengual MJ, Munoz X. Identification of Pen m 4 as a potential cause of occupational asthma to Gammarus shrimp. *Clin Transl Allergy*. 2018;8:46.
79. Flokstra-de Blok B, Brakel TM, Wubs M, et al. The feasibility of an allergy management support system (AMSS) for IgE-mediated allergy in primary care. *Clin Transl Allergy*. 2018;8:18.
80. Neighbour H, Soliman M, Steacy LM, et al. The Allergic Rhinitis Clinical Investigator Collaborative (AR-CIC): verification of nasal allergen challenge procedures in a study utilizing an investigational immunotherapy for cat allergy. *Clin Transl Allergy*. 2018;8:11-15.
81. Panzner P, Vachova M, Vlas T, Vitovcova P, Brodska P, Maly M. Cross-sectional study on sensitization to mite and cockroach allergen components in allergy patients in the Central European region. *Clin Transl Allergy*. 2018;8:19.
82. Zhou Y, Jia H, Zhou X, Cui Y, Qian J. Epidemiology of spider mite sensitivity: a meta-analysis and systematic review. *Clin Transl Allergy*. 2018;8:21.
83. Segboer CL, Terreehorst I, Gevorgyan A, Hellings PW, van Drunen CM, Fokkens WJ. Quality of life is significantly impaired in nonallergic rhinitis patients. *Allergy*. 2018;73(5):1094-1100.
84. Surda P, Putala M, Siarnik P, Walker A, Bernic A, Fokkens W. Rhinitis and its impact on quality of life in swimmers. *Allergy*. 2018;73(5):1022-1031.
85. Hallberg J, Ballardini N, Almqvist C, et al. Impact of IgE sensitization and rhinitis on inflammatory biomarkers and lung function in adolescents with and without asthma. *Pediatr Allergy Immunol*. 2019;30(1):74-80.
86. Schramm D, Reuter M, Grabenhenrich LB, et al. What does lung function tell us about respiratory multimorbidity in childhood and early adulthood? Results from the MAS birth cohort study. *Pediatr Allergy Immunol*. 2018;29(5):481-489.
87. Siroux V, Ballardini N, Soler M, et al. The asthma-rhinitis multimorbidity is associated with IgE polysensitization in adolescents and adults. *Allergy*. 2018;73(7):1447-1458.

88. Lemmetyinen RE, Karjalainen JV, But A, et al. Higher mortality of adults with asthma: a 15-year follow-up of a population-based cohort. *Allergy*. 2018;73(7):1479-1488.
89. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012;50(1):1-12.
90. Cole M, Bandeen-Roche K, Hirsch AG, et al. Longitudinal evaluation of clustering of chronic sinonasal and related symptoms using exploratory factor analysis. *Allergy*. 2018;73(8):1715-1723.
91. Liao B, Liu JX, Li ZY, et al. Multidimensional endotypes of chronic rhinosinusitis and their association with treatment outcomes. *Allergy*. 2018;73(7):1459-1469.
92. Doulaptsi M, Prokopakis E, Seys S, Pugin B, Steelant B, Hellings P. Visual analogue scale for sino-nasal symptoms severity correlates with sino-nasal outcome test 22: paving the way for a simple outcome tool of CRS burden. *Clin Transl Allergy*. 2018;8:32.
93. Munoz-Cano R, Ribo P, Araujo G, Giralt E, Sanchez-Lopez J, Valero A. Severity of allergic rhinitis impacts sleep and anxiety: results from a large Spanish cohort. *Clin Transl Allergy*. 2018;8:23.
94. Camargos P, Affonso A, Calazans G, et al. On-demand intermittent beclomethasone is effective for mild asthma in Brazil. *Clin Transl Allergy*. 2018;8:7.
95. Sharma A, Aalbers R, Hamelmann E, et al. Pharmacokinetics of tiotropium in asthmatic children aged 6–11 years support its safety profile. *Pediatr Allergy Immunol*. 2018;29(7):773-776.
96. Davila I, Dominguez-Ortega J, Navarro-Pulido A, et al. Consensus document on dog and cat allergy. *Allergy*. 2018;73(6):1206-1222.
97. de Araujo PD, de Souza A, Stein RT, et al. Distinct patterns of CD4 T-cell phenotypes in children with severe therapy-resistant asthma. *Pediatr Allergy Immunol*. 2019;30(1):130-136.
98. Maio S, Baldacci S, Bresciani M, et al. RItA: the Italian severe/uncontrolled asthma registry. *Allergy*. 2018;73(3):683-695.
99. Tanaka H, Nakatani E, Fukutomi Y, et al. Identification of patterns of factors preceding severe or life-threatening asthma exacerbations in a nationwide study. *Allergy*. 2018;73(5):1110-1118.
100. Keskin O, Arik Yilmaz E, Motzkus C, Sackesen C, Lilly CM, Kalayci O. The effect of montelukast on early-life wheezing: a randomized, double-blinded placebo-controlled study. *Pediatr Allergy Immunol*. 2018;29(1):50-57.
101. Hu J, Chen J, Ye L, Cai Z, Sun J, Ji K. Anti-IgE therapy for IgE-mediated allergic diseases: from neutralizing IgE antibodies to eliminating IgE(+) B cells. *Clin Transl Allergy*. 2018;8:27.
102. Casale TB, Chipps BE, Rosen K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy*. 2018;73(2):490-497.
103. Skypala IJ, de Jong NW, Angier E, et al. Promoting and achieving excellence in the delivery of Integrated Allergy Care: the European Academy of Allergy & Clinical Immunology competencies for allied health professionals working in allergy. *Clin Transl Allergy*. 2018;8:31.
104. Guarnaccia S, Quecchia C, Festa A, et al. Evaluation of a diagnostic therapeutic educational pathway for asthma management in youth. *Pediatr Allergy Immunol*. 2018;29(2):180-185.
105. Bachert C, Bousquet J, Hellings P. Rapid onset of action and reduced nasal hyperreactivity: new targets in allergic rhinitis management. *Clin Transl Allergy*. 2018;8:25.
106. Bousquet J, Arnavielhe S, Bedbrook A, et al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. *Clin Transl Allergy*. 2018;8:45.
107. Kortekaas Krohn I, Callebaut I, Alpizar YA, et al. MP29-02 reduces nasal hyperreactivity and nasal mediators in patients with house dust mite-allergic rhinitis. *Allergy*. 2018;73(5):1084-1093.
108. Van Gerven L, Steelant B, Alpizar YA, Talavera K, Hellings PW. Therapeutic effect of capsaicin nasal treatment in patients with mixed rhinitis unresponsive to intranasal steroids. *Allergy*. 2018;73(1):248-250.
109. Hong H, Wang D, Tan KS, et al. Sinus computed tomography predicts clinical response to corticosteroids in chronic rhinosinusitis with nasal polyps. *Clin Transl Allergy*. 2018;8:24.
110. Mosges R, Bachert C, Panzner P, et al. Short course of grass allergen peptides immunotherapy over 3 weeks reduces seasonal symptoms in allergic rhinoconjunctivitis with/without asthma: a randomized, multicenter, double-blind, placebo-controlled trial. *Allergy*. 2018;73(9):1842-1850.
111. Mosges R, Kasche EM, Raskopf E, et al. A randomized, double-blind, placebo-controlled, dose-finding trial with Lolium perenne peptide immunotherapy. *Allergy*. 2018;73(4):896-904.
112. Rondon C, Blanca-Lopez N, Campo P, et al. Specific immunotherapy in local allergic rhinitis: a randomized, double-blind placebo-controlled trial with *Phleum pratense* subcutaneous allergen immunotherapy. *Allergy*. 2018;73(4):905-915.
113. Mosges R, Koch AF, Raskopf E, et al. Lolium perenne peptide immunotherapy is well tolerated and elicits a protective B-cell response in seasonal allergic rhinitis patients. *Allergy*. 2018;73(6):1254-1262.
114. Pfaar O, Lang S, Pieper-Furst U, et al. Ultra-short-course booster is effective in recurrent grass pollen-induced allergic rhinoconjunctivitis. *Allergy*. 2018;73(1):187-195.
115. Huber S, Lang R, Steiner M, et al. Does clinical outcome of birch pollen immunotherapy relate to induction of blocking antibodies preventing IgE from allergen binding? A pilot study monitoring responses during first year of AIT. *Clin Transl Allergy*. 2018;8:39.
116. Masuyama K, Okamoto Y, Okamiya K, et al. Efficacy and safety of SQ house dust mite sublingual immunotherapy-tablet in Japanese children. *Allergy*. 2018;73(12):2352-2363.
117. Okamoto Y, Fujieda S, Okano M, Hida H, Kakudo S, Masuyama K. Efficacy of house dust mite sublingual tablet in the treatment of allergic rhinoconjunctivitis: a randomized trial in a pediatric population. *Pediatr Allergy Immunol*. 2019;30(1):66-73.
118. Kother J, Mandl A, Allekotte S, et al. Early nonreactivity in the conjunctival provocation test predicts beneficial outcome of sublingual immunotherapy. *Clin Transl Allergy*. 2018;8:28.
119. Ihara F, Sakurai D, Yonekura S, et al. Identification of specifically reduced Th2 cell subsets in allergic rhinitis patients after sublingual immunotherapy. *Allergy*. 2018;73(9):1823-1832.
120. Martinez-Canavate Burgos A, Torres-Borrego J, Molina Teran AB, et al. Molecular sensitization patterns and influence of molecular diagnosis in immunotherapy prescription in children sensitized to both grass and olive pollen. *Pediatr Allergy Immunol*. 2018;29(4):369-374.
121. Toftlund LH, Agertoft L, Halken S, Zachariassen G. Improved lung function at age 6 in children born very preterm and fed extra protein post-discharge. *Pediatr Allergy Immunol*. 2019;30(1):47-54.
122. Yu J, Liu X, Li Y, et al. Maternal exposure to farming environment protects offspring against allergic diseases by modulating the neonatal TLR-Tregs-Th axis. *Clin Transl Allergy*. 2018;8:34.
123. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy*. 2017;72(8):1156-1173.
124. Nilsson S, Odling M, Andersson N, Bergstrom A, Kull I. Does asthma affect school performance in adolescents? Results from the Swedish population-based birth cohort BAMSE. *Pediatr Allergy Immunol*. 2018;29(2):174-179.
125. Campbell AP, Hoehle LP, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. Depressed mood is associated with loss of productivity in allergic rhinitis. *Allergy*. 2018;73(5):1141-1144.
126. Yong YV, Shafie AA. Economic evaluation of enhanced asthma management: a systematic review. *Pharm Pract (Granada)*. 2014;12(4):493.

127. Muraro A, Fernandez-Rivas M, Beyer K, et al. The urgent need for a harmonized severity scoring system for acute allergic reactions. *Allergy*. 2018;73(9):1792-1800.
128. Cardona V, Demoly P, Dreborg S, et al. Current practice of allergy diagnosis and the potential impact of regulation in Europe. *Allergy*. 2018;73(2):323-327.
129. Kidon M, Blanca-Lopez N, Gomes E, et al. EAACI/ENDA Position Paper: diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. *Pediatr Allergy Immunol* 2018;29(5):469-480.
130. Kortekaas Krohn I, Shikhagaie MM, Golebski K, et al. Emerging roles of innate lymphoid cells in inflammatory diseases: clinical implications. *Allergy*. 2018;73(4):837-850.
131. Gerth van Wijk R, Eguiluz-Gracia I, Gayraud J, et al. The roadmap for allergology in Europe: the subspecialty of allergology as "stopover" on the way to a full specialty. An EAACI position statement. *Allergy*. 2018;73(3):540-548.
132. Jensen-Jarolim E, Bax HJ, Bianchini R, et al. AllergoOncology: opposite outcomes of immune tolerance in allergy and cancer. *Allergy*. 2018;73(2):328-340.
133. Brockow K, Ardern-Jones MR, Mockenhaupt M, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. *Allergy*. 2019;74(1):14-27.
134. Dona I, Caubet JC, Brockow K, et al. An EAACI task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity. *Clin Transl Allergy*. 2018;8:16.
135. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy*. 2016;71(2):149-161.
136. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414.
137. Augé J, Vent J, Agache I, et al. EAACI Position paper on the standardization of nasal allergen challenges. *Allergy*. 2018;73(8):1597-1608.

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