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Developments in the field of allergy in 2016 through the eyes of Clinical and Experimental Allergy

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Abstract

In this paper we described the development in the field of allergy as described by Clinical and Experimental Allergy in 2016. Experimental models of allergic disease, basic mechanisms, clinical mechanisms, allergens, asthma and rhinitis and clinical allergy are all covered.

Abbreviations: AAD, allergic airway disease; AD, atopic dermatitis; AHR, airway hyperresponsiveness; ASC, antibody secreting cell; GC, goblet cell; Bet-APE, aqueous birch pollen extracts; APCs, antigen-presenting cells; DC, dendritic cell; HDM, house dust mite; IL, interleukin, IL1RL1, Interleukin 1 Receptor Like 1; IFN, interferon; LMW, low molecular weight; IOM, Institute of Medicine; OVA, ovalbumin, WHO, Th, T helper cell; TSLP, Thymic stromal lymphopoietin; World Health Organization; SPT, skin prick test (SPT); SCF, stem cell factor; ILC, innate lymphoid helper cell; PALMs, pollen-associated lipid mediators; Tregs, regulatory T cells.

Mechanisms of Allergic Disease

Beyond the allergen: coimmunomodulators in allergic responses

Pollens

Pollen is one of the most common causes of allergies, and it is thought that at least 40% of patients with allergies worldwide are sensitized to grass pollen allergens¹⁻³. More than 150 pollen allergens, originating from grasses, trees, and weeds, are officially acknowledged by the IUIS allergen nomenclature sub-committee⁴. However, recent studies indicate that pollen grains contain additional protein and non-protein substances, beyond the allergen content, that have immunomodulatory activity; these substances include oxidases, proteases, pollen-associated lipid mediators (PALMs), and adenosine^{5,6}. Oxidases, including ragweed pollen NADPH oxidase, stimulate reactive oxygen species, alter airway epithelial function, and can induce allergic airway inflammation in experimental animal models^{7,8}. PALMs, which consist of monohydroxylated products of linoleic and linolenic and resemble human leukotrienes, modulate human neutrophil and eosinophil migration and dendritic cell (DC) activation^{5,6}. Adenosine stimulates CD4⁺ T cell priming⁹. Are these allergen-coincident immunomodulators clinically relevant?

Gilles-Stein and colleagues recently analyzed the birch pollen metabolome in a protein-free, low molecular weight (LMW) fraction of aqueous birch pollen extracts (Bet-APE < 3 kDa) and identified numerous LMW compounds including lipids, hormones, sugars, and purine and pyrimidine nucleosides⁹. Ultraperformance liquid chromatography (UPLC) analyses identified the presence of adenosine in the micromolar concentration and that it was ubiquitously present in aqueous extracts of several pollens including birch, grass, ragweed, and pine pollen but not mugwort pollen. Notably, the authors demonstrated that pollen-derived adenosine stimulated an A2 receptor-dependent induction of cAMP and inhibited IL-12p70 induction in DCs, suggesting potent immunoregulatory activity⁹. In a follow-up study, Gilles-Stein and colleagues¹⁰ now report that these birch pollen-derived LMW compounds amplified

allergen-specific immune responses in humans *in vivo*. The authors showed that skin prick test (SPT) reactions to pollen elicited larger wheals when allergens (native Phl p 1) were tested together with the LMW compounds from pollen. Notably, similar results were obtained with candidate PALMs, including linoleic acid derivatives contained in aqueous pollen extracts of birch—9-HODE, 13-HODE, 9-HOTE, and 13-HOTE. The authors went on to show that nasal challenge of patients with allergies with an allergen (Phl p 1) plus Bet-APE < 3 kDa also increased the levels of cytokine production (IL-8) and IgE in the nasal lining fluids of patients allergic to birch and grass pollen. Notably, these patients had increased nasal secretion and reported more severe rhinorrhea than the group challenged with allergen only. Importantly, neither the Bet-APE < 3 kDa nor the linoleic acid derivatives induced any cutaneous allergic responses in the absence of allergen¹⁰. These data suggest that LMW compounds from pollen are not sufficient to induce an allergic response but can enhance the allergen-specific immune response in the skin and nose and are therefore of potential clinical relevance in patients with allergies. This knowledge will help to understand mechanisms of sensitization and sharpen therapeutic strategies involving pollen extracts.

Costimulatory molecules in allergic sensitization and the resulting cascade

The induction of pollen sensitization is thought to be mediated by DC presentation of pollen allergens to naïve CD4⁺ T cells in the draining lymph nodes, which promotes the development of an allergen-specific CD4⁺ type 2 response and orchestration of the allergic inflammatory cascade including allergen-specific IgE and mast cell (MC)- and eosinophil-dominant responses^{11,12}. A critical step for the DC–CD4⁺ type 2 cell polarization was the interaction of co-stimulatory molecules (CD28 and CD80/CD86; OX40L and OX40) between antigen-presenting cells (APCs) and T cells¹³. Recent studies indicate that interaction of APC-expressed OX40L and T cell–expressed OX40 is important for CD4⁺ Th₂ polarization and immune responses^{14,15}. Recent studies by Linhart and colleagues examined the effect of CD28 and CD40L neutralization by monoclonal antibody on IgE sensitization and development of allergic disease. Employing a major timothy grass pollen allergen Phl p 5 allergy model, the authors demonstrated that blockade of CD40L (alone or together with CTLA4Ig) during the primary sensitization prevented the development of Phl p 5–specific Ig response and immediate-type reactions¹⁶. The suppressive effects of anti-CD40L (anti-CD154) blockade were temporary and persisted until re-exposure to the same allergen. Anti-CD40L treatment of Phl p5–sensitized mice during the secondary allergen challenge phase had no effect on allergic secondary IgE responses¹⁶. Blocking CD28 (with CTLA4Ig) either during the sensitization or secondary allergen challenge phase had no detectable influence on the humoral response¹⁶. Thus, though ‘conventional’ costimulation blockade suppressed the development of allergen-specific IgE during the primary antigen exposure, it did not lead to lasting tolerance¹⁶. In a follow-up study, the authors investigated whether blocking OX40 alone or in addition to ‘conventional’ costimulation blockade (anti-CD40L/CTLA4Ig) prevents a timothy grass Phl p 5–induced IgE-mediated allergic responses. The authors demonstrated that OX40L blockade alone during the primary or secondary antigen exposure phase did not inhibit the development of Phl p 5–specific IgE-mediated responses, which was consistent with the observed inability of anti-OX40L to inhibit established CD4⁺ Th responses

in adults with mild asthma¹⁷. The authors also examined the effect of OX40L/CD40L/CD28 blockade on primary and secondary Phl p5-specific responses. The authors showed that OX40L/CD40L/CD28 blockade during the secondary challenge phase had little effect on Phl p 5-specific Ig responses; however, treatment during the primary sensitization phase caused a significant delay in the development of allergen-specific responses. Notably, the delayed response was associated with decreased T cell proliferation and mediated by CD25⁺ T regulatory cells (Tregs). The authors concluded that OX40L, CD40L, and CD28 neutralization can suppress allergic T cell responses. The studies suggest that (murine) T cell and B cell responses towards a major grass pollen allergen do not depend on OX40L/OX40 costimulatory signals and that combined costimulation blockade (OX40L/CD40L/CD28) is required for suppression of allergen-specific Ig responses and that it involves Treg-mediated suppression.

The fungal factor: modeling fungal influences in allergic disease

The Institute of Medicine (IOM) and World Health Organization (WHO) have identified potential adverse health outcomes and respiratory health effects from fungal bioaerosols in contaminated buildings in the general population¹⁸⁻²². Furthermore, it is well established that chronic exposure to fungal particles can also exacerbate pre-existing respiratory distress and lead to rhinitis, asthma, and allergic diseases²³⁻²⁵. A significant limitation to understanding the impact of chronic fungal exposure on respiratory health and in understanding of the immunopathologic pathways involved in the fungal-induced respiratory complications and exacerbation of allergic cascades has been the lack of appropriate animal models of fungal exposure. Experimental model systems have been developed in which mice are exposed to either fungal spores or crude antigen extracts in liquid suspensions or dry fungal bioaerosols. However, there are limitations with these models, including delivery of a large bolus of spores, dosage control of inhaled fungal particles, and usage of anesthesia, which is thought to influence natural fungal deposition in the lung and lead to a disease phenotype that does not consistently reproduce the pulmonary pathology associated with chronic exposures²⁶.

To address these methodologic limitations, Buskirk and colleagues developed an acoustical generator system (AGS) for delivering dry aerosolized fungal spores to mice housed in a multi-animal exposure chamber²⁷. Aerosolized spores are delivered into a nose-only inhalation chamber, where mice inhale the spores. Employing this system, the authors previously demonstrated that short-term inhalational exposures of mice (4 weeks) to *Aspergillus fumigatus* (*A. fumigatus*) induced a significant pulmonary cellular infiltrate dominated by CD8⁺ IL-17A⁺ (Tc17) T cells, which correlated with spore germination²⁷. In a follow-up study, Nayak and colleagues now report that a 13-week subchronic exposure of BALB/cJ mice with *A. fumigatus* spores induced a different immunopathologic phenotype²⁸. Moreover, the authors show that a 13-week subchronic exposure (total 26 exposures) of *A. fumigatus* B-5233 spores led to fungal deposition in murine lungs primarily localized in the lung interstitium²⁸. Notably, the repeated exposures of *A. fumigatus* spores resulted in a dose-dependent and multifocal peribronchial and perivascular inflammation characterized by mononuclear phagocytes, granulocytes, and lymphocytes and

concomitant epithelial mucus hypersecretion, goblet cell metaplasia, subepithelial fibrosis, and enhanced airway hyperresponsiveness (AHR). Interestingly, in contrast to the short course exposure²⁷, the pulmonary infiltrate was predominately consisted of CD4⁺ IL-13⁺ T cells and an antifungal CD4⁺ IFN γ ⁺ IL-17A⁺ IL-13⁺ T cell response, revealing a dynamic shift in the dysregulated immune response following subchronic exposure of inhaled fungi. Understanding the signals involved in the oscillation of these CD4⁺ T cell populations between anti-fungal/allergic Th1, Th2, Th17 phenotypes will provide a better understanding of the underlying pathways that contribute to the fungal association with allergic disease.

Immune mechanisms of allergic airway disease

Allergen exposure of the pulmonary epithelium stimulates epithelial cell-derived production of cytokines such as TSLP, IL-25, and IL-33, which are thought to launch the proallergic type 2 cytokine response through activation of innate lymphoid type 2 cells (ILC2) and CD4⁺ Th2 T cells^{12,29}. The ILC2- and CD4⁺ Th2 cell-derived type 2 cytokines IL-4, IL-5, IL-9, and IL-13 promoted IgE production and engagement of IgE with Fc ϵ RI on basophils and MCs; IL-5 and IL-9 promoted tissue eosinophilia and MC hyperplasia; and IL-13 promoted mucus production by goblet cells and AHR, which are hallmark clinical manifestations of allergic asthma³⁰.

IL-33 and ST2: differential processes in allergic airway disease

Experimental studies in mouse models have revealed that administration of IL-33 results in a prototypic type 2 cytokine response leading to secretion of IgE, pulmonary eosinophilia, mucus production, and AHR³¹. Consistent with these data, allergen challenge of IL-33 receptor IL-1RL1- or IL-33-deficient mice lead to a diminished pulmonary allergic inflammatory response and impaired AHR^{32,33}. Zoltowska and colleagues examined the role of IL-33/ST2 signaling in promoting the allergen-induced asthma phenotype in a murine model of asthma³⁴. The authors showed that exposure of WT or ST2-deficient (ST2^{-/-}) BALB/c mice to house dust mite (HDM) extract for a 6-week period induced the asthma phenotype (AHR, airway inflammation, antigen-specific IgE production, and MC activation). Importantly, the authors revealed HDM-induced AHR in both the central airways and peripheral lung. Consistent with previous studies, HDM challenge of ST2^{-/-} mice induced a milder asthma phenotype with reduced pulmonary infiltrate (eosinophils and myeloid cells), GC hyperplasia, MC activation, and HDM-specific IgE. The reduction in the inflammatory phenotype was associated with reduced prototypic type 2 cytokine production. Interestingly, the authors revealed that ST2 deficiency was associated with diminished HDM-induced AHR in the peripheral lung, whereas AHR in the central airways was unaffected and comparable to WT mice. Consistent with this observation, the inflammatory response (cellular infiltration) was reduced in the peripheral airways of HDM-treated ST2^{-/-} mice³⁴. These data suggest a role for the IL-33/ST2 pathway in the induction of peripheral inflammation and mucus production that causes AHR in the peripheral lung. The authors speculate that the observed IL-33/ST2-dependent effects on the peripheral airways may be explained by the heightened presence of IL-33-secreting alveolar airway epithelial cells, alveolar macrophages, and type II alveolar pneumocytes and by the presence of ST2-expressing inflammatory

cells in the peripheral lung compartment. Consistent with this concept, levels of HDM-induced IL-33 in WT mice were elevated in the parenchyma compared with central airways³⁴. These studies reveal a distinct role for IL-33/ST2 signaling in allergic airway inflammation and AHR between the proximal and peripheral airways and suggest differential mechanisms that regulate AHR in different pulmonary compartments. Given that asthma is considered to be a small airway disease, these observations may have important implications for understanding the immunologic processes that regulate peripheral versus central airway dysfunction in asthma.

Inhibiting airway inflammation and remodeling

A major histopathologic manifestation of asthma is the onset of airway remodeling, which is thought to contribute to the irreversible, or partially reversible, airflow obstruction and ultimately unresponsiveness to asthma therapies such as corticosteroids³⁵⁻³⁷. Airway remodeling refers to the morphologic changes of the airways of individuals with asthma; these changes include the loss of epithelial integrity, subepithelial fibrosis, GC hyperplasia, smooth muscle hypertrophy, and increased airway vascularity³⁸⁻⁴¹. Roflumilast is a selective, small-molecule phosphodiesterase 4 (PDE4) inhibitor that has been shown to possess anti-inflammatory and fibrotic capabilities and is the first PDE4 inhibitor approved for treatment of chronic obstructive pulmonary disease (COPD)^{42,43}. Selective inhibition of PDE4 increases cellular cAMP, reducing immune cell inflammatory processes including chemotaxis, activation, and degranulation, and has been shown to reduce inflammation-induced airway remodeling^{44 42,45}. Kim and colleagues employed a mouse model of chronic asthma to determine the effect of roflumilast on the development of the manifestations of asthma (airway inflammation, remodeling [GC hyperplasia and pulmonary fibrosis], and AHR)⁴⁶. The authors showed that chronic intranasal exposure of ovalbumin (OVA)-sensitized BALB/c mice with OVA administration twice a week for 3 months induced the asthma phenotype. Administration of roflumilast during intranasal allergen exposure significantly inhibited airway inflammation (cellular infiltration and cytokine production) and AHR. Notably, the reduction in inflammation was associated with airway remodeling. Mechanistic in vitro analyses revealed that roflumilast treatment significantly inhibited stem cell factor (SCF)-induced cell proliferation of fibroblasts. Consistent with this observation, the level of SCF was significantly decreased in mice following roflumilast treatment. These studies suggest that the administering roflumilast regulates airway inflammation, AHR, and airway remodeling in asthma possibly via suppression of the SCF/c-KIT pathway.

Allergen-specific immunotherapy: the weight of IgG

There is clinical and experimental evidence to support a role for the dosage of allergen exposure as a contributing factor to IgE sensitization and allergic disease⁵⁷⁻⁵⁹. One possible explanation for the reduced risk of allergy with exposure to high doses of some allergens is the induction of “blocking antibody,” namely allergen-specific IgG. Consistent with this argument, data from animal-based studies show that high-dose intraperitoneal injection of antigens with the adjuvant alum leads to a high antigen-specific IgG and low IgE response, whereas low-dose injection induces a greater IgE response and a lower IgG

response^{60,61}. Hirai and colleagues employed a mouse model system whereby mice were cutaneously sensitized to *Dermatophagoides pteronyssinus* dust mite extract (HDM) to examine the relationship of the dosage of cutaneous allergen exposure, development of IgG- and IgE-specific immune responses, and allergen sensitization⁶². The authors showed that epicutaneous exposure of NC/Nga mice to various doses of HDM induced a dose-dependent exacerbation of atopic dermatitis (AD)-like skin lesions that was associated with elevated HDM-specific IgG and IgE. Notably, the mice exposed to low doses of HDM demonstrated increased susceptibility to HDM-specific IgE and anaphylaxis, and adoptive transfer of total IgG from HDM-sensitized mice reduced the susceptibility seen in mice exposed to low doses of HDM. The authors concluded that high-dose cutaneous exposure to HDM induced effective, blocking IgG production, despite being accompanied by IgE production. The authors used NC/Nga mice, which have a genetic skin barrier defect related to low ceramide production⁶³, which may limit extrapolation of these conclusions to individuals with skin-barrier defects. Furthermore, though the authors demonstrated that allergen-specific IgG can act effectively inhibit IgE responses in mice, IgG4 antibody subtype is thought to be the primary blocking antibody in humans; mice lack this antibody subtype⁶⁴. However, these data support the clinical observations in allergen-specific immunotherapy, that increases in IgG titer, not a decrease in IgE titer, is a better marker of clinical improvement in allergen-specific immunotherapy.

Food allergy and anaphylaxis

Transferring peanut allergy: a newly discovered role of B cells

Recently, clinical reports have been emerging of the transfer of food allergy to tolerant individuals who receive solid organ and bone marrow transplants from donors with peanut allergy⁴⁷⁻⁵⁴. Currently, the underlying molecular basis for the onset of peanut allergy in these previously tolerant individuals is poorly understood. Moutsoglou and Dreskin⁵⁵ developed a murine adoptive transfer model to begin to determine the cellular requirements for the transfer of murine peanut allergy (PNA) and the role B cells play in maintaining long-lived anti-peanut IgE levels. The authors employed an adoptive transfer model system whereby naïve C3H/HeJ mice were irradiated and subsequently received splenocyte populations from PNA mice that were depleted of either CD3⁺, CD19⁺, or B220⁺ cells. The recipient mice subsequently received intraperitoneal challenge with crude peanut extract to examine for evidence of peanut allergen sensitization. The authors revealed that adoptive transfer of purified splenic B220⁺ cells from PNA mice was not sufficient to transfer the PNA phenotype. In contrast, transfer of both purified splenic B220⁺ and CD4⁺ T cells from PNA mice was sufficient to adoptively transfer PNA phenotype. Surprisingly, transfer of purified splenic B220⁺ cells from PNA mice and splenic CD4⁺ T cells from non-allergic mice also transferred the PNA phenotype. Given the requirement for B220⁺ cells from PNA-exposed mice and PNA or non-allergic CD4⁺ T cells to transfer the PNA phenotype, the authors speculated a requirement for CD20⁺ B populations for maintaining long-lived, anti-peanut allergen-specific IgE. To test this, the authors treated PNA mice with anti-CD20 antibody for 18 weeks, which resulted in the >94% depletion of peripheral blood, splenic, bone marrow, and peritoneal B cell populations. Notably, there was no effect on B220⁺ cells within the bone marrow; however, the remaining bone marrow CD19⁺ cells were primarily of

early B cell lineage. Surprisingly, the prolonged and severe depletion of mature B cells did not significantly affect anti-peanut allergen-specific IgE levels nor induction of the anaphylactic phenotype, indicating that prolonged B cell depletion does not abrogate PNA. Analyses of bone marrow and splenocytes revealed that anti-CD20 treatment had no effect on long-lived, IgE⁺ antibody-secreting cells (ASCs) in the bone marrow. To determine whether the anti-CD20-resistant B cell populations can maintain serum peanut allergen-specific IgE levels, bone marrow and splenic cells from PNA donors treated with anti-CD20 or control antibody were transferred into naïve recipients. Notably, recipient mice that received bone marrow and splenic cells from PNA donors treated with anti-CD20 antibody did not develop an anti-peanut allergen-specific IgE response or PNA following secondary exposure with crude peanut extract. These studies indicate that the B cell populations that survive depletion with anti-CD20 antibody are not capable of forming IgE⁺ ASCs and transferring the PNA. These studies show that PNA can be established in a non-allergic recipient after transfer of peanut allergen-specific B and T cells from a PNA donor. Furthermore, though long-term depletion of B220⁺ cells with anti-CD20 antibody does not affect anti-peanut allergen IgE levels, it does prevent the transfer of the PNA phenotype in recipient mice. There are some limitations of these studies, including the intraperitoneal challenge route of the crude peanut extract, which will stimulate both a IgG- and IgE-mediated anaphylactic response⁵⁶. However, these results highlight a novel role for B cells in the development of PNA and provide evidence that long-lived, anti-peanut allergen IgE levels may be maintained by long-lived ASCs.

Birch pollen immunotherapy in food and pollen allergen immunologic cross-reactivity

Recent clinical data from Northern and Central Europe indicate a relationship between food allergy and IgE sensitization to pollen allergens such as birch pollen allergy⁶⁵. Birch pollen-related food allergy is thought to be a consequence of immunologic cross-reactivity between ubiquitous birch pollen (BP) allergens (Bet v1, Bet v2, and Bet v6) and structurally related food proteins⁶⁶. For example, Bet v1-specific IgE antibodies have been shown to cross-react with homologous proteins identified in different stone fruits, including apple, cherry, and pear; hazelnut; celery; and carrot⁶⁶. Conversely, approximately 50-93% of patients with pollen allergy experience allergic symptoms following consumption of these cross-reactive BP-related foods⁶⁷. For nearly two decades immunotherapy approaches (subcutaneous and sublingual) have been used to treat patients with birch pollen allergy with excellent efficacy and tolerance⁶⁸⁻⁷¹; however the effectiveness of BP allergen-specific immunotherapy on suppressing accompanying cross-reactive allergies is unclear. To begin to address this, Utsch and colleagues utilized a recently developed mouse model of birch pollen allergy to investigate the efficacy of birch pollen immunotherapy on the cross-reactivity to the homologue apple allergen Mal d1. The authors previously demonstrated that intraperitoneal exposure to alum-adsorbed birch pollen extract (BPE) and subsequent exposure to BPE induced BP allergy that was associated with Bet v1-specific IgE and respiratory allergy⁷². In the recent study, the authors showed that intraperitoneal exposure to alum-adsorbed BPE and subsequent exposure to BPE led to the development of anaphylaxis. Interestingly, the development of BP allergy was associated with the development of Mal d1-specific IgE following systemic Mal d1

exposure. Subcutaneous birch pollen immunotherapy (BP SCIT) of BP-allergic mice protected the mice against an anaphylactic response to systemic challenge with Mal d1. These studies suggest that BP immunotherapy may ameliorate the sensitization to cross-reactivity proteins identified in different stone fruits such as apple (Mal d1). The molecular mechanism of BP SCIT-mediated suppression of Mal d1 sensitization was not fully delineated. The authors showed that BP SCIT decreased Mal d1-specific IgE and increased levels of the inhibitory immunoglobulin Mal d 1-specific IgG_{2a}. Notably, this was associated with decreased Mal d1-mediated MC degranulation. These data suggest that increased inhibitory immunoglobulin, such as IgG_{2a}, may drive the Mal d1 protective response. In support of these experimental findings, development of Bet v1 IgG4 in human BP SCIT studies is associated with better efficacy to improve oral allergy syndrome to apple⁷³⁻⁷⁵.

Food-dependent, nonsteroidal anti-inflammatory drug-induced anaphylaxis

There is emerging clinical evidence supporting the notion that nonsteroidal anti-inflammatory drugs (NSAIDs) can act as a cofactor and exacerbate food-induced allergic reactions⁷⁶. In food-dependent, NSAID-induced anaphylaxis (FDNIA), NSAIDs are the only cofactor required to enhance the allergic reaction^{77,78}. Currently, we do not fully understand the underlying molecular basis for FDNIA; however, it is currently postulated that NSAID-enhancement of food allergy responses is mediated in part by increased gastrointestinal permeability, which is thought to increase food allergen absorption and/or amplify MC and basophil degranulation and mediator release^{77,79,80}. Pascal and colleagues recently evaluated the effect of both lysine acetylsalicylate (L-ASA) (non-selective cyclooxygenase (COX) inhibitor) and valdecoxib (selective COX-2 inhibitor) on basophil activation in patients with peach allergy (Pru p3) and FDNIA. The authors stratified individuals with Pru p3 allergy into two groups: 1) *non-NSAID*, patients with a clinical history of anaphylaxis as caused by Pru p3 without the involvement of NSAIDs and 2) *FDNIA*, patients with a clinical history of anaphylaxis to Pru p3 that only occurred when the culprit food was consumed in proximity to the ingestion of an NSAID (up to 2 hours before/after the reaction onset); for the FDNIA group, anaphylaxis was not reported after peach ingestion or NSAID alone. Employing a flow cytometry-based basophil activation test (BAT), the authors showed that basophil sensitivity and reactivity (as assessed by CD63 expression) to Pru p3 was greater in the non-NSAID group than the FDNIA group. Exposure of basophils from both non-NSAID and FDNIA individuals to both Pru p3 and L-ASA led to a comparable increase in basophil activation; however, COX-2 inhibitor (valdecoxib) exposure reduced Pru p3-induced activation of basophils from the FDNIA group. In contrast, COX-2 inhibitor exposure of basophils from the non-NSAID group had a biphasic response; moreover, high concentrations of valdecoxib inhibited Pru p3-induced activation, whereas low concentrations of valdecoxib enhanced basophil activation. These data suggest that basophils from individuals with non-NSAID anaphylaxis and those with FDNIA possess different reactivity and sensitivity to allergen activation and suggest that NSAIDs directly act on basophils and modulate activation. The observed increase of in vitro sensitivity and reactivity of basophils in non-NSAID anaphylaxis is consistent with the different

severity of the reactions observed in these patients following challenge with peach alone. One potential explanation for these differences is the increased Pru p3-specific serum IgE observed in the non-NSAID group. Interestingly, the authors observed increased basophil activation induced by Pru p3 (as means of CD63 expression) in both the non-NSAID and FDNIA groups following L-ASA exposure. The potentiation of the basophil activation by NSAIDs suggests the existence of a universal phenomenon affecting individuals with allergies that can be clinically relevant depending on the NSAID dose, the allergen concentration, or other concurrent circumstances. The exact mechanism underlying food allergy induced by NSAID remains unknown; however, these findings suggest a role of alteration in the COX pathway.

Allergens

House dust mite

Knowledge of the physicochemical and immunological properties of allergens continues to expand. In general, inhalant allergens have been highly characterized, as exemplified by house dust mite (HDM), which now boasts 36 protein allergens for *Dermatophagoides spp.*, according to the WHO/IUIS Allergen Nomenclature Subcommittee (www.allergen.org). Among the newer allergens described, Der p 23 is arguably most noteworthy, based on the high proportion of subjects with HDM allergy (>70%) who have specific IgE to this allergen⁸¹. In work reported in the journal, Mueller and colleagues confirmed this finding, despite a low abundance of Der p 23 relative to Der p 1 and Der p 2, in RNA from mite cultures⁸². Nonetheless, levels of serum IgE to Der p 23 were lower compared with other HDM allergens, and Der p 23 accounted for only a small percentage of the IgE response to dust mite. Structural analysis using X-ray crystallography revealed similarities between Der p 23 and other allergens that bind chitin via carbohydrate binding domains, though no chitin binding could be verified for Der p 23. These findings suggest that more work is needed to understand the relative contributions of HDM allergens to clinical disease.

Food allergens

The rise in food allergies has provided impetus for various facets of molecular research related to food allergens. In particular, the relevance of linear versus conformational IgE epitopes has been widely debated. Chen and colleagues reported on conformational IgE epitopes for the homologous peanut allergens, Ara h 2 and Ara h 6⁸³. This was accomplished by screening a phage 12mer peptide library with affinity-purified specific IgE antibodies from peanut-allergic patients, verifying antibody binding of the resulting candidate mimotopes among a larger group of patients by ELISA, and then determining molecular localization by computer-based mapping. Those mimotopes identified were deemed to be conformational based on their localization on the molecular surface and lack of a match for linear amino acid sequences within peanut allergens. Moreover, while a small number of mimotopes were recognized by the majority of sera from peanut allergic patients, IgE binding patterns were heterogeneous and did not relate to IgE levels to peanut or clinical history. In a different study, profiles of conformational IgE

epitopes of the soya bean allergen Gly m 4 were identified⁸⁴. That approach involved using multiple recombinant variants consisting of a non-IgE binding model protein engrafted with Gly m 4 residues, in order to systematically identify those epitopes that might account for Gly m 4-mediated birch pollen allergy. The results showed that more than 80% of total IgE binding capacity of Gly m 4 could be accounted for by 6 IgE-binding regions; however, there was no correlation between serum levels or avidity of specific IgE, and clinical reactivity, when comparing sensitized subjects with clinical allergy versus tolerance to soya bean. Thus, while these two studies highlight the advances in molecular methods for mapping putative functional IgE epitopes, they also illustrate the enigmatic relationship between allergen-specific IgE profiles and clinical disease.

Other molecular studies in the journal focused on allergen cross-reactivity. Wangorsch and colleagues tested IgE binding to the recombinant forms of the plane pollen allergen, Pla a 3, and the peach allergen Pru p 3, among patients who were allergic to either plane pollen, peach, or both⁸⁵. The findings supported a role for Pla a 3, but not the major allergen Pla a 1, in peach allergy, and the potential usefulness of this component in IgE testing as a diagnostic tool for peach allergy. Additional work at the T-cell epitope level has shed light on the degree of cross-reactivity among different tree nuts⁸⁶. This was accomplished by first mapping epitopes of the major cashew allergens Ana o 1 and Ana o 2, using an *in vitro* assay that detects allergen-specific CD4+ T cells based on their rapid activation by antigenic peptides. Analysis of T-cell specificity using MHCII tetramers revealed a subset of cashew epitopes that cross-reacted with hazelnut and/or pistachio, but not walnut. The findings imply that a peptide vaccine using cashew peptides may confer some level of cross-protection against allergy to other tree nut allergens, but not walnut.

IgE antibodies against galactose- α -1,3-galactose (a-Gal) have been associated with severe anaphylactic reactions with first use of cetuximab and delayed anaphylactic reactions with red meat. Villalta and colleagues have found a high prevalence of sIgE to a-Gal in people living in a rural village in the Italian Alps where there is a high exposure to ticks⁸⁷. Further work is required to look at whether they are symptomatic with red meats.

There is strong evidence for the induction of tolerance to food allergens via the oral route. Intriguing new data from a randomized controlled trial suggested that maternal egg ingestion influences the concentration of ovalbumin in breastmilk, and links to serum levels of egg-specific IgG4 in lactating infants⁸⁸. This infers that maternal diet can influence the development of tolerance in children during an early window.

Once food allergy is established, oral immunotherapy strategies should minimize IgE binding to avoid side effects, while retaining the capacity to activate T cells in order to induce tolerance. To this end, Tao

and colleagues used mass spectrometry to monitor allergen peptides that resulted from boiling raw peanuts⁸⁹. Boiling for 12 hours was optimal for reducing IgE binding, and generated short peptides (7-28 amino acids in length) spanning significant regions of major allergens. Notably, the resulting peanut preparation activated T cells to a similar degree as non-boiled raw peanut in cultures from peanut-allergic subjects. In a mouse model of shrimp allergy, oral administration of T-cell epitopes of the major shrimp allergen, Met e 1, resulted in reduced specific IgE, as well as reduced eosinophils and goblet cells in the gut⁹⁰. In tandem, increased blocking antibodies in the serum and enhanced expression of Th1/Treg-associated genes in the intestine were observed. These studies highlight the potential value of allergen-derived peptides to mitigate food allergy.

Epidemiology

Exposure during pregnancy

During the last decades there has been a substantial focus on the foetal uterointerine environment in relation to onset of allergy related diseases in the offspring. During 2015 a number of scientific reports on this topic were published in our journal. So also during 2016.

PUFA: In a paper from the Generation R Study the associations of maternal fatty acid levels during pregnancy with airway resistance and inflammation, asthma and eczema in school-age children were studied.⁹¹ Almost 5 000 mothers and their children were included in a population-based prospective cohort study. Plasma levels of glycerophospholipid fatty acid were during the second trimester of pregnancy and at the age of 6, airway resistance and inflammation were measured as well as exhaled nitric oxide (FeNO). Current physician- diagnosed asthma and eczema were assessed. Higher maternal total PUFA and total n-6 PUFA levels were associated with a significant decreased risk of childhood asthma but with an increased risk of childhood eczema. The observed associations were partly explained by Linoleic acid (LA, C18:2n-6) levels. Maternal total n-3 PUFA levels and n-6/n-3 PUFA ratio were not associated with current asthma and eczema. No consistent associations of maternal total polyunsaturated fatty acid (PUFA), total n-6 PUFA, total n-3 PUFA levels and n-6/n-3 PUFA ratio during pregnancy were associated with child's Rint and FeNO. What the authors pointed out in this study was that intervention studies on time for publication of this report have been scarce and inconclusive, mostly due to small sample size, variability in dose and duration of supplementation, delay in the beginning of the supplementation during pregnancy or lactation, lack of variability in maternal dietary patterns and short time period of follow-up. They concluded that new large randomized controlled trials using PUFA supplements from the earliest phases of pregnancy were needed.

Vitamin D: The research group behind the Generation R cohort also investigated the associations of maternal and fetal 25-hydroxyvitamin D levels with childhood lung function and asthma.⁹² For this study

data of a little more than 3 000 mothers including maternal blood samples in mid-gestation and umbilical cord blood samples at birth were used to determine 25-hydroxyvitamin D levels. Data on outcome was collected as mentioned above. Low levels of 25-hydroxyvitamin D at birth were associated with a higher airway resistance in childhood. Additional adjustment for child's current 25-hydroxyvitamin D level reduced the effect size of the association and no associations of 25-hydroxyvitamin D levels in mid-gestation or at birth with FeNO, wheezing patterns, or asthma were observed. From this paper and also from the current global scientific literature on this topic, there seems still to be an open question whether vitamin D possible interrupt the regulatory mechanisms or not.

Antibiotics: Another area of interest has been the use of antibiotics during pregnancy or early infancy and its impact of development childhood asthma due to the influence of antibiotics on the microbiota. In also a Dutch study a case-sibling survey of 1 228 children with asthma and their 1 228 non-asthmatic siblings was undertaken.⁹³ Prescription of asthma medication was used as a proxy for asthma by the use of a representative prescription database including a mother-infant subset of approximately 40 000 mothers and their children. The influence of confounding was controlled for. Antibiotic use in the third trimester of pregnancy was associated with a small increased risk of asthma in preschool children. The association was robust to time-invariant confounding or exposure time trends, further supporting the important role for early-life intestinal microbiota in the development of childhood asthma.

Vitamin B3 (nicotinamide) and tryptophan: within the UK Southampton Women Survey. Serum levels of kynurenine, kynurenic acid, anthranilic acid, tryptophan, nicotinamide and N1-methylnicotinamide of 497 mothers were measured in late pregnancy and related to the odds ratio of infantile atopic eczema. at ages 6 and 12 months.⁹⁴ Higher concentrations of nicotinamide and anthranilic acid were associated with a lower risk of eczema at age 12 months. The associations were robust to adjustment for potentially confounding variables. Their findings point to potentially modifiable maternal influences on this complex and highly prevalent condition of atopic eczema during infancy.

Prenatal exposure to persistent organic pollutants: Persistent organic pollutants (POPs) are a diverse class of organohalogen compounds. The production and use of many of these chemicals have been severely restricted and in some cases banned for several decades, but humans are still exposed via the diet, primarily through the consumption of fatty fish. POPs bioaccumulate in human and animal adipose tissue and are can be transported across the placental barrier. In a Danish survey the effect of such prenatal exposure to persistent organic pollutants and offspring allergic sensitization and lung function at 20 years was studied.⁹⁵ Almost 50 % of the originally eligible subjects participated in the follow up. They found an indication that prenatal exposure to POPs seemed to be associated with airway obstruction but not allergic sensitization 20 years after exposure and the authors argue that chronic obstructive lung

diseases may have at least part of their origins in early life and may influence respiratory health throughout the life course.

Maternal age: Abid and colleagues have examined asthma in an American study⁹⁶. Their results adds more complexity to the maternal age/offspring asthma associations which are already complex and now in this study reveal opposite associations amongst Mexican American mothers compared to Caucasian mothers with a protective effect of young maternal age in this Latino group. Further study is required to untangle possible reasons for the association in this group.

Ethnicity

Several interesting paper on migration and development of allergy related diseases has been published from Australia. Last year in Clinical and Experimental Allergy, Kate Allen and the team around her published reported on nut allergy prevalence differences between Asian-born children and Australian born children with Asian descent.⁹⁷ For their study they used School Entrant Health Questionnaire administered to all 5-yearold children in Victoria, Australia. The prevalence of parent-reported nut allergy (tree nut and peanut) was assessed and whether this was altered by region of residence, socioeconomic status, country of birth or history of migration. They found that parent-reported nut allergy was more common among children born in Australia of Asian-born mothers than non-Asian children. Children born in Asia who subsequently migrated to Australia were at decreased risk of nut allergy. Parental migration from Asia to Australia appears to be an important risk factor in the development of nut allergy in the next generation, while being born in Asia is protective even with migration to Australia in early life.

In Denmark differences in hospital attendance for anaphylaxis between immigrants and non-immigrants were investigated in a cohort.⁹⁸ A register-based, historical prospective cohort study was designed. Refugees or family reunified immigrants (n = 127 250) who obtained residency permits in Denmark were included and matched in a 1 : 6 ratio on age and sex with Danish-born individuals (n = 740 600). Personal identification numbers were cross-linked to the Danish National Patient Registry identifying all first-time hospital attendances for anaphylaxis (1994-2010). Incidence of anaphylaxis was estimated. In total 1053 hospital attendances for anaphylaxis were identified. Non-Western immigrants had a significantly lower risk ratio of hospital attendance for anaphylaxis compared to Danish-born. Compared to Danish-born, non-Western immigrants living in Denmark during the entire follow-up period also showed a decreased risk. Compared to Danish-born, non-Western immigrants who obtained residence permission as children had a decreased risk of hospital attendance for anaphylaxis. However, this protection was lost during the follow-up period. Therefore, the authors conclude that information on the burden of anaphylaxis and its variations with time, place, and person is important to understand disease aetiology, but also for ensuring

adherence to evidence-based anaphylaxis guidelines in clinical management and patient support for persons at risk of this potentially life-threatening event.

Furry animals

In a Swedish cross sectional study of adults 20-46 years and with data collected 2009-2012 the results of that data collection was compared to similar data collected from the same region and with the same age groups from 1991-1992, thus at least 17 years apart.⁹⁹ Between the two study periods there was a significant increase in pollen sensitization whereas sensitisation to other inhalant allergens remained unchanged. There was a significant reduced risk of any allergic sensitisation of growing up with livestock or furred pets. Growing up with livestock reduced the risk of sensitisation to pollen allergens, or any of cat, dog or horse allergens. The limitation of this study, in relation to risk factor analysis, is its cross sectional design and retrospective collection of data which is also pointed out by the authors.

Exposure to foods

In the Swedish population based birth cohort study BAMSE of 4000 the incidence, characteristics and associated risks of anaphylaxis to foods among 16 year olds.¹⁰⁰ They found that the incidence of food-induced anaphylaxis during adolescence in our population-based birth cohort was higher than previously reported. Adolescents with anaphylaxis differ from adolescents with non-anaphylactic food related symptoms with regard to culprit foods and sensitization. Adolescents with previous anaphylaxis were likely to be polysensitized to foods, particularly tree nut and peanut storage proteins, and which warrants consideration at clinical follow-up.

Asthma and rhinitis

Exhaled nitric oxide and eosinophils

Giovannelli and colleagues have demonstrated that both exhaled nitric oxide and blood eosinophil count are associated with mild allergic asthma, but only in non-smokers. They have revisited the FeNO and blood eosinophilia/allergic asthma relationships in smoking and non-smoking asthmatics and shown that these two allergic asthma markers are non-discriminatory in asthmatics currently smoking¹⁰¹. Smoking status needs to be considered when these markers are being used in research or clinical evaluations of asthmatics.

Mogensen and colleagues have shown that simultaneously elevated exhaled nitric oxide and serum-eosinophil cationic protein are related to recent asthma events in asthmatics in a cross-sectional population-based study¹⁰². Simultaneously elevated FeNO and ECP (controlling for current smoking) were associated with more symptoms and exacerbations of asthma with each marker contributing independently to symptoms and exacerbations respectively. As in other studies this further supports the value of FeNO when combined with other markers of allergic asthma.

In a detailed study of lung nitric oxide dynamics amongst sensitised workers following challenge with isocyanates, Mason and colleagues demonstrated that the delayed rise in exhaled NO is from increased flux from the airway wall to the lumen rather than alveolar production and was confined to those exposed and who showed a constrictor response¹⁰³. The clinical upshot is that monitoring simple exhaled NO should be a good a marker of isocyanate inflammation.

Finally, Al-shamkhi and colleagues have confirms that the previously reported environmental and demographic factors that influence FeNO in healthy populations also apply to those with mild asthma¹⁰⁴. Two novel additional factors, age of menarche and parental smoking also appear to lower FeNO in this population. Overwhelmingly though atopy appears to be the major driver of FeNO in this population from the Swedish GA2LEN study.

Bronchial hyperresponsiveness

Sverrild and colleagues have related mannitol and methacholine airway responsiveness to specific mast cell phenotypes (specifically tryptase and chymase positive mast cells) and mannitol AR to eosinophilic airway inflammation in the submucosa in ICS free asthmatics¹⁰⁵. It is not clear though if these associations are causal. If they prove to be causally associated this would suggest that mannitol AHR might be a more useful marker of eosinophilic airway inflammation than methacholine or other direct agents.

Biomarkers

There is a rapidly growing literature on the search for new useful serum and salivary biomarkers of asthma. Clusterin is a ubiquitous antioxidant glycoprotein. In a study by Soi and colleagues¹⁰⁶, salivary levels of clusterin were elevated in asthmatic children compared to controls and levels were positively correlated with clinical severity particularly children with eosinophilic asthma. Interestingly salivary levels were reduced in children with asthma exacerbations possible related to clusterin 'consumption' by oxidants or the use of systemic corticosteroids. This effect may reduce the clinical value of clusterin as an asthma marker.

Periostin is now one of the more studied asthma biomarkers. In this population, Caswell-Smith and colleagues explore normal ranges (wide) in an adult population without asthma or COPD¹⁰⁷. Median levels in this population were similar to previous studies amongst subjects with asthma and severe asthma suggesting that periostin is not driven by asthma related pathology and is not a useful marker of disease or disease severity.

Psychological factors

That asthma is both depressing and anxiety inducing has been the subject of a number of studies and perhaps is not all that surprising. In a large twin study from the Swedish Twin Register, Tedner and colleagues largely confirm these previous findings and are able to demonstrate that the effect is not likely to be genetic or due to environment and probably not related to ICS treatment¹⁰⁸.

Severe asthma

Cluster analyses are being brought to bear on more complex clinical issues. In this paper Seikiya and colleagues confirm previous observations that severe asthma exacerbations arise in clusters with underlying severity, in those with multiple co-morbidities especially amongst women, those not using ICS and interestingly amongst symptomatically mild patients who had had a previous hospital admission for asthma, one of the strongest predictors of severe exacerbations¹⁰⁹.

In a longitudinal study of severe poorly controlled asthma, Walsh and colleagues showed that sputum eosinophilia (but not sputum neutrophilia) is a strong predictor of asthma exacerbations¹¹⁰. This supports the clinical experience with these severe allergic patients. The neutrophil findings, or neutrophil phenotype, may be a marker of previous eosinophilic asthma that is better treated, or with better adherence or response to corticosteroids.

In a Xolair registry study, Hew and colleagues reported that 31% of patients were above the 750mg dosing range (by weight and/or IgE) which would exclude them in some jurisdictions and mean that they would receive higher doses in other jurisdictions¹¹¹. This study suggested that these patients benefit equally using the 750mg cut off and that they should be included and that higher doses may not be required.

Finally, Song and colleagues show that in older patients with asthma (≥ 65 years and many specifically with chronic rhinosinusitis and nasal polyps), IgE to staphylococcal enterotoxin was associated with an increased risk of more severe disease and disease associated with sputum eosinophilia¹¹². In this elderly late onset group sensitisation to these specific antigens seem to be particularly important as has been shown in younger severe asthmatics. A key question is can this insight be useful therapeutically?

Experimental challenge models

Since Spieksma, Voorhorst and colleagues first used climate chambers to study dust allergy in the 1960s there has been interest in the use of chambers in this and the occupational asthma setting. Kenney and colleagues illustrates the new precision with which this can now be done dialling up an exact and well distributed pollen count that is highly reproducible and measuring it regularly in real time and showing the associated clinical effects¹¹³.

Air Pollution

In this large single city study over a decade, Chen and colleagues present data showing that increments of a variety of air pollutants and pollens were associated with increased hospital admission¹¹⁴. This was especially seen with PM_{2.5} (30% increase in admissions for a 10 unit increase) and a far greater effect in children compared to adults. These effects are also related to season and temperature which differ for different pollutants. There was no obvious interaction between pollens and pollutants as has been found in other studies. Presumably the future maybe real time risk predictions that can be met with increased treatment.

Clinical allergy

Food allergy and Anaphylaxis

Milk allergy guidelines are frequently published, much more so than other food allergy guidelines – perhaps due to the high impact of milk allergy on individual dietary regimes, but possibly also due to the importance of milk allergy for commercial concerns. With this in mind, Ruszczynski's assessment of milk allergy guidelines using the AGREE II tool is of interest¹¹⁵. The authors identified significant variation in guideline quality, with highest quality seen for guidelines produced by professional organisations such as BSACI, WAO or EAACI. Deschildre and colleagues, reporting findings from the MIRABEL peanut allergy study, confirmed earlier observations from the UK that severity of reaction is associated with age – adolescents and young adults had the highest rate of severe reactions, compared with younger children¹¹⁶. The MIRABEL study authors then went on to use cluster analysis to group peanut allergy patients by clinical phenotype – further publications from this interesting observational study are keenly awaited¹¹⁷. In one of the most comprehensive reviews of fatal anaphylaxis in recent years, Mullins et al described 16 years of Australian data¹¹⁸. They reported an apparent increase in fatal anaphylaxis rates, in contrast to recent UK and US findings – and highlighted upright posture as being associated with such cases, and a number of other risk factors specific to each trigger – for example most fatal food anaphylaxis occurred between the ages of 17 and 45 years. Although this journal has previously reported a low risk of fatal anaphylaxis for people with food allergy, Hanna et al showed community healthcare professionals overestimate this risk by approximately 1 log¹¹⁹. This may have implications for the way we discuss risk with patients affected by food allergy. Norman et al¹²⁰ showed that advice to eat nuts to which a child is not allergic was not followed at home, perhaps due to anxiety about the possibility of a severe reaction occurring in the home environment – however a supervised food challenge was followed by home introduction in most cases.

Allergy Diagnosis

A significant proportion of clinical allergy services is devoted to making an accurate diagnosis, and the value of this is sometimes called into question. In a randomised controlled trial of allergy testing and

appropriate allergen avoidance advice, for children aged 6 to 16 years with allergic rhinoconjunctivitis or asthma, Smith and colleagues identified clear, measurable improvements in rhinitis symptoms and quality of life 1 year after the intervention¹²¹. Thus supporting the value of allergy testing, when combined with appropriate interpretation and avoidance advice.

Diwakar and colleagues¹²² audited diagnosis and management of hymenoptera venom allergy within UK National Health Service clinics, in relation to BSACI guidelines¹²³. They found reasonable adherence to the guidance, but a notable variation in adherence to the recommendation to use skin testing as the first line investigation. Hence allergists are not consistently using the most reliable testing method for hymenoptera allergy. In this context, it is interesting to note that a study from Slovenia found evidence that component testing for bee venom (rApim1) and yellow jacket wasp venom (rVesv5) using recombinant LITE products, performed well compared with ImmunoCAP recombinant allergens, or native allergens – this potentially avoids the issue of cross-reactive carbohydrate determinants which has been reported with use of native allergens for venom IgE testing¹²⁴. However, as with many previous reports of IgE testing in different scenarios, no comparison with skin testing was made, which is the current first line investigation according to BSACI guidance. Moreover the authors found no association between IgE levels and severity of reaction. Where skin and intradermal testing is not contra-indicated, it remains the preferred diagnostic test for hymenoptera allergy due to its high sensitivity.

Kespohl and colleagues¹²⁵, studying mould allergy, found improved diagnostic sensitivity from skin prick testing than from specific IgE testing, consistent with findings in relation to other allergic diseases. Diagnosis of perioperative anaphylaxis can also be difficult, and Egner and colleagues¹²⁶ highlighted several specific issues with the sensitivity of current mast cell tryptase assays in their review of 17 years of UK data. Burk and colleagues, reporting immunological findings from a study of peanut sublingual immunotherapy, found a prognostic role for IgE allergy tests – they showed that lower specific IgE to peanut, to Ara h2 or to Ara h3 were all associated with increased probability of successful desensitisation during treatment¹²⁷.

Drug allergy and urticaria

In a retrospective review of allergy testing following apparent immediate-type reactions to iodinated contrast media, Sese and colleagues found a reasonable negative predictive value from skin prick and intradermal testing – however they did identify patients who appeared to pass an intravenous challenge test, but later reaction to contrast media again¹²⁸. This supports international recommendations to consider repeat allergy testing in patients with a high likelihood of drug allergy (at least for beta-lactam allergy), including drug provocation testing, even if they pass the initial challenge test¹²⁹. Park and colleagues highlighted ranitidine as a cause of anaphylaxis, which in their experience was often overlooked due to the presumption that this drug is not a common cause of allergic reactions – however

the authors report on 584 cases, including 99 with anaphylaxis¹³⁰. Another significant cause of drug allergy is chlorhexidine – Opstrup and colleagues¹³¹ found that most patients with chlorhexidine allergy have positive specific IgE 1 to 4 months post-reaction, and that although specific IgE declines after this time, this does not necessarily mean the drug allergy has resolved, with cases recorded of recurrent reaction years later despite negative specific IgE.

Maurer and colleagues, in a systematic review of the literature, found good evidence for an association between chronic spontaneous urticaria and systemic lupus erythematosus¹³². In the majority of cases urticarial preceded the diagnosis of systemic lupus erythematosus, thereby justifying screening for lupus in patients presenting with chronic spontaneous urticarial – however the authors caution that the evidence base is insufficiently strong to reliably quantify the association between these disorders at present.

Jepsen and colleagues¹³³ reported data from the COPSAC cohort studies showing that a breast milk inflammatory mediator pattern dominated by interleukin 1 beta was associated with reduced risk of eczema in offspring. This is not the first report of breast milk analytes associated with altered inflammatory disease risk in infants, but there is little consistency in outcomes or replication of findings in this area of study to date.

Conclusions

The year 2016 was another interesting year in the field of allergy with advances across our understanding across many areas. We look forward to further interesting data in 2018.

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