

YEAR IN REVIEW

Developments in the field of clinical allergy in 2015 through the eyes of Clinical and Experimental Allergy

G. Roberts^{1,2,3}, R. Boyle⁴, P. J. Bryce⁵, J. Crane⁶, S. P. Hogan⁷, S. Saglani⁸, M. Wickman⁹ and J. A. Woodfolk¹⁰

¹Clinical and Experimental Sciences and Human Development and Health, Faculty of Medicine, University of Southampton, ²NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, ³The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, ⁴Paediatric Research Unit, Imperial College London, London, UK, ⁵Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, ⁶Department of Medicine, University of Otago Wellington, Wellington, New Zealand, ⁷Division of Allergy and Immunology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, OH, USA, ⁸National Heart & Lung Institute, Imperial College London, London, UK, ⁹Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden and ¹⁰Allergy Division, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA, USA

Clinical & Experimental Allergy

Summary

In the second of two papers, we describe developments in the field of clinical allergy as documented by Clinical and Experimental Allergy in 2015. Epidemiology, clinical allergy, asthma and rhinitis are all covered.

Correspondence:

Professor Graham Roberts, Paediatric Allergy and Respiratory Medicine (MP803), Clinical & Experimental Sciences & Human Development in Health Academic Units, University of Southampton, Faculty of Medicine & University Hospital Southampton, Southampton SO17 1BJ, UK.

E-mail: g.c.roberts@soton.ac.uk

Cite this as: G. Roberts, R. Boyle, P. J. Bryce, J. Crane, S. P. Hogan, S. Saglani, M. Wickman and J. A. Woodfolk, *Clinical & Experimental Allergy*, 2016 (46) 1389–1397.

In this second of two reviews, we discuss the new findings in the field of allergy in 2015 focusing on clinical aspects. These highlight the contribution published in Clinical and Experimental Allergy. We focus on epidemiology, clinical allergy, asthma and rhinitis.

Epidemiology

General

The research field of allergy-related diseases is complex since we often lack firm data on exposure, and outcome is not easy to estimate as diagnosis is often

more subjective compared to other disease areas. Additionally we lack high-quality registries. Such registries are based on a doctor's willingness to enter patient data. Such registers give us a good description of entered patients although we do not know what data are excluded. However, the situation is improving with i-technology. In some EU countries, there are now inpatient, outpatient and national registers including registers for twins. However, a lot of information for epidemiological research in the field of allergy related diseases is still based on questionnaire data, where the quality of the collected information is not always known.

Methodology

Questionnaires are an efficient tool for assessing outcomes of interest in epidemiological studies. These are usually undertaken in large population-based studies. Reports of symptoms at exposure for allergens have often been taken as proxies for hypersensitivity to that allergen. For allergy to foods, it has been suggested that oral challenges are needed to establish a diagnosis of food allergy and that a questionnaire report in combination with an allergy test is not sufficient. Chu *et al.* [1] demonstrated good agreement (83.0–89.5%) between specific triggers and specific results from skin prick testing (SPT). However, when atopy, defined as at least one positive skin test of a panel of aeroallergens, was compared to current hay fever or eczema, the sensitivity of the questionnaire variables was generally low (19.3–32.2%), while the specificity was higher (77.5–94.0%). The authors summarize that questionnaires remain important, efficient and sometimes the only way to collect medical information in a large study sample. Given the good specificity and the negative predictive value, the authors suggest that questionnaire may constitute an efficient tool for risk factor epidemiological studies that involve the differential inclusion of subjects without atopy. Although its use inevitably leads to some misclassification, questionnaires deliver a more rapid and cost-effective method of measuring allergic status in population-based studies than SPT or the use of other objective means.

Prevalence rates – time trends

In a paper by Patil *et al.* [2], the authors aimed at assessing time trends of wheeze, rhinitis and aero-allergen sensitization prevalence at 10 years of age by comparing two birth cohorts established 12 years apart. To gain insight into differences in disease prevalence, they assessed association of family history, early life exposures and sensitization with wheeze and rhinitis in each cohort. The IoW (Isle of Wight) and FAIR (Food Allergy and Intolerance Research, also from Isle of Wight) unselected birth cohorts were established in 1989 and 2001, respectively. Identical questionnaires were used and skin prick test data were collected and compared at 10 years of age in both studies. Contrasting and significant changes were noted with falling wheeze/ever treatment for asthma and HDM sensitization but rising rhinitis and grass sensitization prevalence. The authors suggest that changing prevalence of aero-allergen sensitizations may explain the different time trends observed in these cohorts. But as the authors write, changes in sensitization are likely to reflect changes in exposure. It is tempting, however, to speculate about the causes of such possible changes in exposure to

grass pollen and to house dust mites since it provides an insight into the possibilities of risk reduction.

Pre- and perinatal factors

In recent years, it has been suggested that prenatal factors have an important role in the development of allergic disease, as the pre- and perinatal periods include critical developmental stages of the respiratory tract and the immune system. Gestational age and birthweight have been suggested as factors that are associated with later asthma development. Twins, as compared to singletons, are on average more likely to be born with lower gestational age and birthweight and have been hypothesized to comprise a high-risk population for asthma. Furthermore, the protective effect of acquiring a healthy gut microbiome in early life has been suggested to affect immune system development at a young age and to partially explain the associations with childhood allergies and allergies. Prenatal antibiotic use has also been found to be of importance in this context. A high maternal pre-pregnant body mass index (BMI) as well as estimated body fat mass has been linked to asthma, asthma symptoms, medication use and respiratory hospitalization in the offspring. However, previous studies have firstly not always been able to adjust for overweight in the child and secondly not formally tested whether the child's BMI could be a mediator in the association between maternal overweight and offspring asthma.

Ullemar *et al.* [3] investigated the association between twinship and childhood asthma or early life wheeze and identify potential mediators, such as gestational age and birthweight (GA/BW). The study population consisted of two cohorts including all children born in Sweden between 1993 and 2001 ($n = 756\,363$ singletons, $n = 22\,478$ twins) and from 2005 to 2009 ($n = 456\,239$ singletons, $n = 12\,872$ twins). Asthma was defined using validated register-based outcomes of diagnosis or medication. Twins were at significantly higher unadjusted risk of asthma or early life wheeze compared with singletons in the younger but not in the older cohort. Associations attenuated following adjustment for GA/BW, suggesting that GA/BW mediates the effect of twinship on asthma risk. After adjustments, twins were at lower risk of asthma outcomes, possibly due to unmeasured confounding.

In a study from Detroit, Wegienka *et al.* [4] used prenatal charts of women enrolled in the WHEALS birth cohort. They were reviewed for delivery mode and medications prescribed and administered throughout their entire pregnancy, including systemic antibiotics and vaginally applied antifungal medications. The associations between the delivery mode and select medications and eczema sensitization (≥ 1 of 10 allergen-specific

IgE ≥ 0.35 IU/mL) and total IgE at age 2 years were assessed. Children born vaginally had lower risk of eczema and sensitization compared with those born via Caesarean section. The authors also propose that the reduced risk with eczema could have been slightly weakened when mothers took systemic antibiotics or vaginally applied medications during pregnancy.

In a study from Hong Kong, Leung et al. [5] examined the association of mode of delivery with hospitalizations for asthma and other wheezing disorders in their offspring in a developed non-Western setting. Public hospital admissions for asthma, bronchitis and bronchiolitis from 9 days to 12 years of age were monitored in a population-representative prospective birth cohort of 8327 children. Caesarean section was not clearly associated with hospitalizations for asthma and other wheezing disorders in children aged 12 years or under. The authors speculate that the observed lack of positive associations of delivery by Caesarean section with childhood wheezing disorders may vary according to the setting and may not be biologically mediated. Thus, and as the authors conclude, further studies with different designs are needed to clarify the role of the microbiome and mode of delivery in the aetiology of asthma and other childhood wheezing disorders.

Asthma and attention-deficit/hyperactivity disorder (ADHD) are both prevalent disorders in childhood and an association between the two conditions has been shown. Almqvist's group from Stockholm, Sweden, aimed to study whether the association between asthma and ADHD was restricted to either the inattentive or the hyperactive/impulsive symptoms of ADHD [6]. For this purpose, they used parental questionnaires at 9 or 12 years on 20, 072 twins through the Swedish Twin Register, linked to the Swedish Medical Birth Register, the National Patient Register and the Prescribed Drug Register. Data on asthma, ADHD, zygosity and possible confounders were collected. They found that childhood asthma, especially severe asthma, was associated with ADHD but use of asthma medication was not. Interestingly, it has recently been shown that there seem to be a link between the gut microbiota and ADHD and studies are now suggesting a gut–microbiota–brain axis.

In the Swedish BAMSE birth cohort, the associations between maternal body mass index (BMI) in pregnancy and offspring asthma, rhinitis, eczema and sensitization up to 16 years of age were observed by Magnusson et al. [7]. A total of 3294 children were included and maternal BMI was assessed around week 10 in pregnancy. Information on asthma, rhinitis, eczema, lifestyle factors and environmental exposures was obtained by repeated questionnaires from 1 to 16 years. Serum-specific IgE was measured. They found that maternal BMI (obese rather than overweight) was positively and significantly associated with an overall risk of asthma

up to the age of 16 years; this was attenuated when adjusting for overweight in the offspring. In contrast, no significant associations were found for rhinitis, eczema or sensitization. A causal inference test at 16 years further indicated that the child being overweight is a mediator in the suggested association between maternal BMI and offspring asthma at 16 years. The authors conclude that prevention strategies of maternal pre-pregnancy and childhood obesity might be important to reduce the prevalence of childhood asthma.

Protective factors – vitamin D

In recent years, vitamin D and its physiological functions have been subjected to increasing interest. Due to its impact on the immune system, vitamin D has been suggested as a potential factor affecting both incidence and severity of asthma and allergic diseases. In recent years, the number of publications of the relationship of vitamin D to asthma and allergic diseases has increased rapidly, but the conclusions of previous studies have been inconsistent. Checkley et al. [8] studied population-based samples of 1441 children in two communities in Peru, of which 1134 (79%) provided a blood sample for 25-OH vitamin D analysis. They found that lower 25-OH vitamin D levels were associated with increased odds of asthma (OR = 1.7 per each 10 ng/mL decrease in 25-OH vitamin D levels). Interestingly and in a stratified analysis, the association between lower 25-OH vitamin D levels and asthma was limited to children with atopy (OR = 2.2, 95% CI: 1.3–3.6) and not in those without. In a paper by Thuesen et al. [9], the authors set out to investigate the association of serum 25-hydroxy vitamin D (25(OH)D) with asthma and atopy in a population of 4999 Danish adults since most previous studies have focused on vitamin D status in early life. The authors summarize that 25(OH)D levels do not seem to influence the development of asthma and allergy among adults and that their results did not consistently support the hypothesis that 25(OH)D levels were associated with lung function. They conclude that randomized controlled trials are needed to further address the role of vitamin D and asthma, including lung function.

Environmental exposure

Exposure to different environmental factors early in life can influence the development of allergy-related diseases and the association between atopy and allergic disease appears to be stronger in affluent compared with non-affluent populations, and in urban compared with rural populations. Urban–rural differences governing the prevalence of environmental exposures that

attenuate atopy could explain these observations. Helminth infections, which are common chronic parasitic infections of predominantly low-income rural populations in the tropics, may have a role in attenuating the association between atopy and allergic symptoms including wheeze. In a paper by Endara *et al.* [10], the authors investigated the associations between atopy and recent wheeze in an urban versus rural residence and in relation to helminth infections versus urban residence in order to determine which environmental exposures including helminth infections might contribute to such an effect. The authors conclude that urban residence may modify the association between HDM sensitization and recent wheeze, and this effect is explained partly by helminth infections.

Food allergy

Martin *et al.* studied which infants with eczema were at risk of challenge-proven food allergy in their population-based Australian HealthNuts Study cohort [11]. One-year-old infants ($n = 4453$ meeting criteria for this analysis) were assessed for history of eczema, receiving a nurse-administered eczema examination and undergoing skin prick testing to peanut, egg and sesame. One in five infants with eczema were allergic to peanut, egg white or sesame, compared with one in twenty-five infants without eczema (OR 6.2, 95% CI: 4.9, 7.9). The prevalence of peanut allergy was low in the absence of eczema (0.7% 95% CI: 0.4, 1.1). Infants with eczema were 11.0 times more likely to develop peanut allergy (95% CI: 6.6, 18.6) and 5.8 times more likely to develop egg allergy (95% CI: 4.6, 7.4) by 12 months than infants without eczema. About 50.8% of infants (95% CI: 42.8, 58.9) with early eczema onset (< 3 months) who required doctor-prescribed topical corticosteroid treatment developed challenge-proven food allergy. This study clearly shows that eczema, across the clinical severity spectrum in infancy, is a strong risk factor for IgE-mediated food allergy. The authors suggest that a heightened awareness of food allergy risk among healthcare practitioners treating infants with eczema, especially if early onset and severe, is warranted.

Peanut allergy may be fatal and receives high coverage in the media where severity of symptoms often is exaggerated. Peanut allergy causes a lot of psycho-social impairment in families with a peanut-allergic child. While previous studies suggest that there is an increased risk of peanut allergy in siblings, more recent studies yield less conclusive results. Further, increasing evidence shows that unnecessary avoidance – because of a fear of an unconfirmed peanut allergy – may actually increase the risk of developing allergy. In a Canadian study, Lavigne *et al.* [12] documented peanut avoidance and peanut allergy diagnosis in siblings of peanut allergy

children. Of 932 registry families, 748 parents, representing 922 siblings, completed a questionnaire on siblings' socio-demographic characteristics, exposure and reaction to peanut; in addition, confirmatory tests were performed to determine whether peanut allergy had been diagnosed. Of the 13.6% of siblings had never been exposed to peanut, 70.4% ($n = 88$) were born after the index child. Almost 9% of siblings (80) were reported as having peanut allergy, but almost half of this group had no history of an allergic reaction to peanut. In a multivariate regression analysis for siblings at least 3 years old, those born after peanut allergy diagnosis in the index child were more likely to have never been exposed to peanut. In a univariate analysis, siblings born after the diagnosis of peanut allergy in the index child were more likely to be diagnosed with peanut allergy without supportive history or confirmatory testing. The authors conclude that educational programmes and guidelines that caution against unnecessary avoidance are required.

Clinical allergy

Food allergy

In a well-designed study in 61 children, Escudero *et al.* [13] showed that a 3-month course of egg oral immunotherapy using 2.8 g protein per week, successfully desensitized 28 of 30 (93%) children; but after a further month without treatment only 11 of 30 (37%) tolerated an egg challenge. This was still significantly higher than in the control group, where egg allergy resolved in just one of 31 (3%) children. However during 3 years of follow-up with *ad libitum* egg intake, three of the 11 successfully treated children reported further symptoms, albeit mild symptoms not requiring treatment. While it is encouraging that this short course of treatment was effective in approximately one-third of participants, achieving higher rates of sustained unresponsiveness and safer, more convenient treatment protocols remain important research goals.

Although a number of studies now document the partial clinical efficacy of oral immunotherapy to foods, the relative role of a sublingual phase to treatment is unclear, especially in adult populations where sublingual placement of food is easier to achieve. One barrier to understanding this is our limited knowledge of the mechanisms underlying oral and sublingual immunotherapy. A murine study by Nagai *et al.* found evidence that egg allergen (ovalbumin) is detected in sublingual ductal epithelial cells within 30 min of administration but is absent by 2 h [14]. This is an area rich in antigen-presenting cells and the finding may help to dissect the mechanisms of oral/sublingual immunotherapy, if the same pathway is relevant in humans.

While many studies focus on children and animals, the findings of the largest study to date of threshold doses to peanut in subjects with peanut allergy by Klemans et al. [15] show that peanut allergy in adults is not exactly the same disease as peanut allergy in children. Here, the authors demonstrate a difference in threshold distribution, although the ED05 was felt to be sufficiently similar to allow general guidance for industry regarding trace peanut labelling.

Understanding how prepared and confident parents feel in managing the food allergies of their children represents an important parameter for healthcare professionals attempting to deliver effective education in clinic. Knibb et al. have developed and validated a new self-efficacy scale for parents of food allergic children [16]. This should be proven a useful outcome measure.

Drug and insect sting allergy

Precise diagnosis of drug and insect sting allergy can be difficult, relying on intradermal skin testing in addition to the specific IgE and skin prick test methodologies used for food and inhalant allergy. Three studies addressed the precision of different approaches to drug and insect sting allergy.

Korosec et al. evaluated the ability of basophil assays to discriminate bee-allergic people with systemic reaction(s), severe systemic reaction(s) or no reaction to ultra-rush up dosing during bee venom immunotherapy [17]. They found that basophil activation assays were able to distinguish between severe systemic reactors and others; this important finding now needs confirmation in a second cohort.

Baker et al. report perhaps the largest series published of immediate-type allergy to corticosteroids [18]. In their series of 23 patients with 28 reactions, almost half of which were to intra-articular corticosteroids, skin prick and intradermal testing were performed at 1 in 10, and up to 1 in 10 dilutions, respectively. Skin testing was positive in those with a history of anaphylaxis but not in those with less severe reactions. They documented the existence of cross-reactivity between corticosteroids (although not commonly) and one case of false-negative skin testing suggesting that follow-up challenges should be considered in such cases. Christiansen et al. studied 89 patients with suspected perioperative cefuroxime allergy, reporting that all confirmed cases had a history of reaction within 15 min of receiving the drug [19]. They used undiluted cefuroxime for the top concentration in skin prick testing and up to a 1 in 100 dilution (0.5 mg/mL) for intradermal testing. Using this protocol, with follow-up provocation tests where possible, they had no false-positive skin tests but did

still have false-negative skin tests. So both drug allergy papers reinforce the importance of considering a follow-up drug provocation test when patients with suspected IgE-mediated drug allergy are found to have negative skin and intradermal test results.

The effect of drugs on allergic disease may not always be as simple as an IgE-mediated allergic reaction. Paracetamol in particular has been hypothesized to increase risk of asthma when used during early life, perhaps by depleting glutathione levels and thereby rendering the host airway vulnerable to oxidant-induced inflammation. An association between paracetamol and asthma has been reported in observational studies including the ISAAC survey and an interesting pilot randomized controlled trial [20] showed that it is possible to randomize infants aged 6–24 months to receive paracetamol more or less frequently, with parents' preferred alternative treatment for randomization being ibuprofen. These encouraging findings should now allow a definitive randomized controlled trial to be designed, which can confirm or refute the paracetamol/asthma hypothesis.

Asthma and rhinitis

Asthma – protective and risk factors

Epidemiological contributions to asthma and allergic disease in Clinical and Experimental Allergy in 2015 include some new insights into old favourites: pets, helminths, aspirin, antibiotics, moulds and siblings and some insights into areas less well traversed: puberty and adolescence.

In the Infant Immune Study cohort from Tucson, Arizona, infant cough persisting for longer than 28 days, or a cough with no cold in the first year of life, was independently associated with future asthma risk, especially in the context of a maternal history of asthma [21]. This adds to what is now a large body of evidence indicating that early abnormalities of airway function predate the development of asthma.

Domestic pets have shown variable and often contradictory associations with asthma and allergy. The ALSPAC birth cohort study is well placed (sufficient numbers and systematic data collection) to look at pets by the timing of exposure and by the type of pet on outcomes at age 7 years. Collin et al. [22] confirms a strong protective effect of pets; halving the risk of atopic asthma and reducing the risk of aeroallergen sensitization but at the cost of an increase in non-atopic asthma particularly for rabbits and rodents. Advice to families regarding pets remains difficult and may become clearer from this cohort when the children are older.

In a nested case control study, Ahumada et al. [23] begin to unravel some of the confusing and long

misunderstood relationship between helminthiasis and asthma. They demonstrate an independent association of ascaris sensitization with asthma in tropical urban environments in Colombia. They show that this association may be at least partially explained by cross-reactivity between ascaris and house dust mite tropomyosins, if true an explanation that fits well with global concepts of the disordered immunology that leads to allergy.

Eriksson *et al.* [24] have measured the prevalence and risk factors for aspirin-intolerant asthma (AIA), a subtype rarely studied epidemiologically using a postal questionnaire survey and random subsample clinical laboratory examination in Western Sweden. AIA was associated with a female preponderance, greater disease severity, obesity (possibly via leukotriene E₄), smoking and self-reported mould exposure but not BHR or FEV₁% predicted and with a marginally lower FeNO. Metsälä *et al.* [25] used linked Finnish national registers to explore antibiotic use by mother and child and asthma among all children born over 8 years in Finland. Both specific prenatal and postnatal antibiotics were strongly associated with asthma with a dose-response relationship. While this study is both large and representative of Finland, it cannot entirely exclude reverse causation and other confounding factors. Damp and mould associations with wheezing and asthma (like antibiotics) have been difficult to unravel and to explain mechanistically. McSharry *et al.* [26] found correlations with a dust-based mould score and % predicted FEV₁ in a small adult asthma study. Interestingly, there were no correlations with reservoir endotoxin, (1,3) β -D-glucans or allergens. Strachan *et al.* [27] in an analysis from the ISAAC phase 3 questionnaire-based study finds both confirmation and a measure of contradiction to his hygiene hypothesis. As in many of the analyses from ISAAC, affluent countries appear different from less affluent with affluence showing a stronger inverse association between siblings and allergic disease than less affluent. By contrast, severe asthma and severe eczema show positive associations with sibship size regardless of affluence.

Puberty and adolescence were featured by asthma in puberty (Hovland *et al.* [28]) and incident wheezing and asthma in adolescence (Hedman *et al.* [29]). Pubertal asthma was associated with early childhood onset and severity, being firstborn and with the number of risk factors before age 2 years and marginally with perinatal family stress. Incident asthma in adolescence was more common in females, first born, among atopic children and those with a parental history. Interestingly, asthma was associated with ever smoking and wheezing with reported house dampness.

These are the only two preventable associations for adolescent or indeed any other asthma.

Until recently, farmyard exposures and microbial products were thought to protect from asthma development. But Behboud and colleagues [30] have shown that elevated levels of bedroom floor yeast in infancy were associated with reduced fungal sensitization and asthma development by school age. Future investigation of the specific fungal components that may be protective may provide an avenue to preventing asthma with fungal sensitization by early life exposure. This is particularly exciting since fungal sensitization is known to cause severe disease in both adults and children.

Asthma and diet

In two studies looking at food and asthma, Berthon *et al.* [31] reassuringly demonstrate no change in appetite, energy intake or weight gain among stable asthmatics receiving 50 mg prednisolone daily for 10 days, while Wood *et al.* [32] examines a newly developed dietary inflammatory index (DII) for macronutrients, vitamins, minerals and bioactives. Higher DII scores (> pro-inflammatory) were associated with asthma, reduced FEV₁ but not increased CRP. Intervention studies of low DII diets appear warranted.

Vocal cord dysfunction

Fowler *et al.* [33] report a new validated questionnaire for symptoms of vocal cord dysfunction (VCD). The instrument was reproducible, reliably distinguishes VCD from normality and is capable of distinguishing clinically useful improvements following treatment.

Allergic rhinitis

Baumann *et al.* [34] in a comparison of two Peruvian urban environments for allergic rhinitis found a higher prevalence in the more urbanized environment, but the difference was explained by the usual personal risk factors, including sensitization and parental history and obesity which accounted for some 10% of the attributable risk.

In a cross-sectional study of allergic conjunctivitis surveying 304 Italian ophthalmologists and 3685 of their patients, Leonardi *et al.* [35] documented redness, itching, tearing and photophobia as the dominant symptoms, seasonal allergens as the dominant triggers, rhinitis in 45%, lid involvement in 11% and keratitis in 11%. Disappointingly only 35% had a diagnostic allergy test, of which over 80% were positive, suggesting that many patients seeing ophthalmologists for allergic conjunctivitis may not be accessing focused advice on allergen avoidance or immunotherapy.

Clinical and Experimental Allergy also published randomized controlled trial data in 2015 demonstrating short-term efficacy for a combined nasal corticosteroid and antihistamine preparation [36] and longer term efficacy for a short course of peptide-based cat immunotherapy [37].

Rhinosinusitis

Several novel findings relating to the pathogenesis of chronic rhinosinusitis with associated nasal polyps (CRSwNP) became apparent in 2015. The equal role of both innate immunity and adaptive immunity were highlighted. Ho et al. [38] demonstrated the presence of increased type 2 innate lymphoid cells and associated eosinophilia in sinus tissue from patients with CRS, with a greater predominance in CRSwNP, suggesting an important role for this innate pathway in disease pathogenesis. In parallel, a key role of myeloid dendritic cells in initiating the downstream adaptive Th2 responses in CRSwNP was demonstrated by Poposki et al. [39]. The balance between regulatory and pro-inflammatory mediators was also shown. Divekar et al. [40] demonstrated an increase in GM-CSF and VEGF in CRSwNP during exacerbation, raising the possibility of targeted therapy during exacerbation, and Xiao and colleagues [41] investigated the hitherto unknown role of IL-21 in CRSwNP. Although commonly considered a regulatory cytokine, IL-21 levels were increased in mucosal polyp tissue and were associated with eosinophilia, greater polyp size and recurrence after surgery, suggesting IL-21 as a marker of more severe disease in patients with CRSwNP. The importance of tissue-specific cells in mediating Th2 responses in allergic rhinitis was demonstrated by the presence of allergen-specific Th2 cells in stable disease, which upon *ex vivo* allergen stimulation using an explant culture model, had the capacity to secrete both IL-5 and IL-13 [42].

Fungal allergens

Fungal allergens are increasingly recognized as having specific properties and the distinction between allergic bronchopulmonary aspergillosis (ABPA) and asthma associated with fungal (aspergillus) sensitization can be hard to make because of difficulties with cross-reactivity of specific IgE antibodies between aspergillus fumigatus and other fungal allergens. Tanimoto et al. [43] therefore measured IgE and IgG antibodies to specific allergen components of aspergillus in the serum of patients with ABPA and asthma with aspergillus sensitization. Aspergillus components Asp f 1 and Asp f 2 were significantly higher in patients that had been

diagnosed with ABPA, confirming measurement of specific allergen components can be used to distinguish disease phenotypes.

Diagnostic testing

Several advances in clinical diagnostic tests were made in 2015. Scadding et al. [44] demonstrated the utility of a nasal cat allergen provocation test that resulted in both local and systemic early (tryptase) and late (Th2 mediators) allergic responses, suggesting such a test could be utilized in future clinical trials of immunotherapy. Advances in the use of non-invasive techniques in children were demonstrated by Brugha et al. [45] who showed induced sputum samples could be used to identify rare immune cells such as dendritic cells in the airways of children, and Arga et al. [46] showed that exhaled nitric oxide was a potential surrogate for a formal airway hyper-responsiveness test in children with atopic asthma. Boulet et al. [47] showed the size of the late asthmatic response after allergen challenge is allergen specific, whereby perennial allergens such as house dust mite induce a stronger late asthmatic response. Thus, suggesting mechanisms mediating the late asthmatic response may also be allergen specific.

Exacerbations

The role of gene mutations in determining therapeutic response to corticosteroids during exacerbations was shown by Vijverberg et al. [48]. SNPs in the ST13 gene (a co-chaperone of the glucocorticoid receptor) were associated with increased exacerbations in children despite maintenance of inhaled corticosteroids. Links between the gut and lung in allergy were reinforced by Iwasaki et al. [49] whereby reduced neutralising antibody responses of the gut echovirus were observed in children with asthma concomitant with exaggerated pro-inflammatory rhinovirus antibody responses.

Conclusions

2015 was another interesting year for Clinical and Experimental Allergy in the field of allergy with advances across asthma, drug allergy, insect allergy, food allergy and rhinitis. Our understanding of clinical allergy has improved with findings from both epidemiological and interventional studies.

Conflict of interest

The authors declare no conflict of interest.

References

- Chu L, Rennie D, Cockcroft D *et al.* Agreement between questionnaire report of allergy-related outcomes in school-age children and objective measures of atopy: the Saskatchewan rural health study. *Clin Exp Allergy* 2015; 45:1337–45.
- Patil VK, Kurukulaaratchy RJ, Venter C *et al.* Changing prevalence of wheeze, rhinitis and allergic sensitisation in late childhood: findings from 2 Isle of Wight birth cohorts 12 years apart. *Clin Exp Allergy* 2015; 45:1430–8.
- Ullemar V, Lundholm C, Almqvist C. Twins' risk of childhood asthma mediated by gestational age and Birth-weight. *Clin Exp Allergy* 2015; 45:1328–36.
- Wegienka G, Havstad S, Zoratti EM, Kim H, Ownby DR, Johnson CC. Combined effects of prenatal medication use and delivery type are associated with eczema at age 2 years. *Clin Exp Allergy* 2015; 45:660–8.
- Leung JYY, Li AM, Leung GM, Schooling CM. Mode of delivery and childhood hospitalizations for asthma and other wheezing disorders. *Clin Exp Allergy* 2015; 45:1109–17.
- Holmberg K, Lundholm C, Anckarsäter H, Larsson H, Almqvist C. Impact of asthma medication and familial factors on the association between childhood asthma and attention-deficit/hyperactivity disorder: a combined twin- and register-based study. *Clin Exp Allergy* 2015; 45:964–73.
- Ekström S, Magnusson J, Kull I *et al.* Maternal body mass index in early pregnancy and offspring asthma, rhinitis and eczema up to 16 years of age. *Clin Exp Allergy* 2015; 45:283–91.
- Checkley W, Robinson CL, Baumann LM *et al.* 5-hydroxy vitamin D levels are associated with childhood asthma in a population-based study in Peru. *Clin Exp Allergy* 2015; 45:273–82.
- Thuesen H, Skaaby T, Husemoen LLN, Fenger M, Jørgensen T, Linneberg A. The association of serum 25-OH vitamin D with atopy, asthma, and lung function in a prospective study of Danish adults. *Clin Exp Allergy* 2015; 45:265–72.
- Endara P, Vaca M, Platts-Mills TAE *et al.* Effect of urban vs. rural residence on the association between atopy and wheeze in Latin America: findings from a case-control analysis. *Clin Exp Allergy* 2015; 45:438–47.
- Martin PE, Eckert JK, Koplin JJ *et al.* Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy* 2015; 45:255–64.
- Lavine E, Clarke A, Joseph L *et al.* Peanut avoidance and peanut allergy diagnosis in siblings of peanut allergic children. *Clin Exp Allergy* 2015; 45:249–54.
- Escudero C, Rodríguez del Río P, Sánchez-García S *et al.* Early sustained unresponsiveness after short-course egg oral immunotherapy: a randomized controlled study in egg-allergic children. *Clin Exp Allergy* 2015; 45:1833–43.
- Nagai Y, Shiraishi D, Tanaka Y *et al.* Transportation of sublingual antigens across sublingual ductal epithelial cells to the ductal antigen-presenting cells in mice. *Clin Exp Allergy* 2015; 45:677–86.
- Klemans JB, Blom WM, van Erp FC *et al.* Objective eliciting doses of peanut-allergic adults and children can be combined for risk assessment purposes. *Clin Exp Allergy* 2015; 45:1237–44.
- Knibb RC, Barnes C, Stalker C. Parental confidence in managing food allergy: development and validation of the food allergy self-efficacy scale for parents (FASE-P). *Clin Exp Allergy* 2015; 45:1681–9.
- Korošec P, Žibera K, Šilar M *et al.* Immunological and clinical factors associated with adverse systemic reactions during the build-up phase of honeybee venom immunotherapy. *Clin Exp Allergy* 2015; 45:1579–89.
- Baker A, Empson M, The R, Fitzharris P. Skin testing for immediate hypersensitivity to corticosteroids: a case series and literature review. *Clin Exp Allergy* 2015; 45:669–76.
- Christiansen IS, Krøigaard M, Mosbech H, Skov PS, Poulsen LK, Garvey LH. Clinical and diagnostic features of peri-operative hypersensitivity to cefuroxime. *Clin Exp Allergy* 2015; 45:807–14.
- Riley J, Braithwaite I, Shirtcliffe P *et al.* Randomized controlled trial of asthma risk with paracetamol use in infancy – a feasibility study. *Clin Exp Allergy* 2015; 45:448–56.
- Oren E, Rothers J, Stern DA, Morgan WJ, Halonen M, Wright AL. Cough during infancy and subsequent childhood asthma. *Clin Exp Allergy* 2015; 45:1439–46.
- Collin SM, Granel R, Westgarth C *et al.* Pet ownership is associated with increased risk of non-atopic asthma and reduced risk of atopy in childhood: findings from a UK birth cohort. *Clin Exp Allergy* 2015; 45:200–10.
- Ahumada V, García E, Dennis R *et al.* IgE responses to *Ascaris* and mite tropomyosins are risk factors for asthma. *Clin Exp Allergy* 2015; 45:1189–200.
- Eriksson J, Ekerljung L, Bossios A *et al.* Aspirin-intolerant asthma in the population: prevalence and important determinants. *Clin Exp Allergy* 2015; 45:211–9.
- Metsälä J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. *Clin Exp Allergy* 2015; 45:137–45.
- McSharry C, Vesper S, Wymer L *et al.* Decreased FEV1% in asthmatic adults in Scottish homes with high Environmental Relative Moldiness Index values. *Clin Exp Allergy* 2015; 45:902–7.
- Strachan DP, Ait-Khaled N, Foliaki S *et al.* Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. *Clin Exp Allergy* 2015; 45:126–36.
- Hovland V, Riiser A, Mowinkel P, Carlsen K-H, Lødrup Carlsen KC. Early risk factors for pubertal asthma. *Clin Exp Allergy* 2015; 45:164–76.
- Hedman L, Andersson M, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. Environmental risk factors related to the incidence of wheeze and asthma in adolescence. *Clin Exp Allergy* 2015; 45:184–91.
- Behbod B, Sordillo JE, Hoffman EB *et al.* Asthma and allergy development: contrasting influences of yeasts and other fungal exposures. *Clin Exp Allergy* 2015; 45:154–63.
- Berthon BS, Gibson PG, McElduff P, MacDonald-Wicks LK, Wood LG. Effects of short-term oral corticosteroid intake on dietary intake, body weight and body composition in adults with asthma – a randomized controlled trial. *Clin Exp Allergy* 2015; 45:908–19.
- Wood LG, Shivappa N, Berthon BS, Gibson PG, Hebert JR. Dietary inflammatory index is related to asthma risk, lung function and systemic

- inflammation in asthma. *Clin Exp Allergy* 2015; 45:177–83.
- 33 Fowler SJ, Thurston A, Chesworth B *et al.* The VCDQ – a Questionnaire for symptom monitoring in vocal cord dysfunction. *Clin Exp Allergy* 2015; 45:1406–11.
- 34 Baumann LM, Romero KM, Robinson CL *et al.* Prevalence and risk factors for allergic rhinitis in two resource-limited settings in Peru with disparate degrees of urbanization. *Clin Exp Allergy* 2015; 45:192–9.
- 35 Leonardi A, Piliego F, Castegnaro A *et al.* Allergic conjunctivitis: a cross-sectional study. *Clin Exp Allergy* 2015; 45:1118–25.
- 36 Murdoch RD, Bareille P, Ignar D *et al.* The improved efficacy of a fixed-dose combination of fluticasone furoate and levocabastine relative to the individual components in the treatment of allergic rhinitis. *Clin Exp Allergy* 2015; 45:1346–55.
- 37 Couroux P, Patel D, Armstrong K, Larché M, Hafner RP. Fel d 1-derived synthetic peptide immuno-regulatory epitopes show a long-term treatment effect in cat allergic subjects. *Clin Exp Allergy* 2015; 45:974–81.
- 38 Ho J, Bailey M, Zaunders J *et al.* Group 2 innate lymphoid cells (ILC2s) are increased in chronic rhinosinusitis with nasal polyps or eosinophilia. *Clin Exp Allergy* 2015; 45:394–403.
- 39 Poposki JA, Peterson S, Welch K *et al.* Elevated presence of myeloid dendritic cells in nasal polyps of patients with chronic rhinosinusitis. *Clin Exp Allergy* 2015; 45:384–93.
- 40 Divekar RD, Samant S, Rank MA *et al.* Immunological profiling in chronic rhinosinusitis with nasal polyps reveals distinct VEGF and GM-CSF signatures during symptomatic exacerbations. *Clin Exp Allergy* 2015; 45:767–78.
- 41 Xiao L, Wei Y, Zhang Y-N *et al.* Increased IL-21 expression in chronic rhinosinusitis with nasal polyps. *Clin Exp Allergy* 2015; 45:404–13.
- 42 Skrinko I, Ballke C, Gran E, Johansen F-E, Baekkevold ES, Jahnsen FL. IL-5 production by resident mucosal allergen-specific T cells in an explant model of allergic rhinitis. *Clin Exp Allergy* 2015; 45:1296–304.
- 43 Tanimoto H, Fukutomi Y, Yasueda H *et al.* Molecular-based allergy diagnosis of allergic bronchopulmonary aspergillosis in *Aspergillus fumigatus*-sensitized Japanese patients. *Clin Exp Allergy* 2015; 45:1790–800.
- 44 Scadding GW, Eifan A, Penagos M *et al.* Local and systemic effects of cat allergen nasal provocation. *Clin Exp Allergy* 2015; 45:613–23.
- 45 Brugha R, Mushtaq N, McCarthy NE, Stagg AJ, Grigg J. Respiratory tract dendritic cells in paediatric asthma. *Clin Exp Allergy* 2015; 45:624–31.
- 46 Arga M, Bakirtas A, Topal E, Turktas I. Can exhaled nitric oxide be a surrogate marker of bronchial hyperresponsiveness to adenosine 5'-monophosphate in steroid-naïve asthmatic children? *Clin Exp Allergy* 2015; 45:758–66.
- 47 Boulet L-P, Gauvreau G, Boulay M-E, O'Byrne PM, Cockcroft DW. Allergen-induced early and late asthmatic responses to inhaled seasonal and perennial allergens. *Clin Exp Allergy* 2015; 45:1647–53.
- 48 Vijverberg SJH, Koster ES, Tavendale R *et al.* ST13 polymorphisms and their effect on exacerbations in steroid-treated asthmatic children and young adults. *Clin Exp Allergy* 2015; 45:1051–9.
- 49 Iwasaki J, Chai LY, Khoo S-K *et al.* Lower anti-echovirus antibody responses in children presenting to hospital with asthma exacerbations. *Clin Exp Allergy* 2015; 45:1523–30.