DOI: 10.1111/cea.13535

REVIEW

WILEY

Developments in the field of clinical allergy in 2018 through the eyes of Clinical and Experimental Allergy, Part II

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Abstract

In this article, we describe developments in the field of clinical allergy as described by Clinical and Experimental Allergy in 2018; epidemiology, asthma and rhinitis, clinical allergy and allergens are all covered.

This review focuses on new findings in the field of epidemiology, asthma and rhinitis, clinical allergy and allergens in 2018. It complements the first year in review which focuses on experimental models of allergic disease, basic mechanisms and clinical mechanisms in 2018.

1 | EPIDEMIOLOGY

In 2018, several highly interesting publications in the area of clinical and respiratory epidemiology have been published in Clinical and Experimental Allergy. Many papers have focused on pregnancy and early life risk factors for subsequent asthma, eczema and food allergies. Although few of those may change clinical practice per se, they will hopefully be combined with other available papers to create evidence-based guidelines with advice to pregnant couples and parents. Other publications have focused on phenotype definitions, time trends and interactions of genes and the environment.

1.1 | Antenatal exposures

The association between exposures preconception or during pregnancy and subsequent asthma or allergic disease is of great interest, and this year has seen several papers in the area.[1] As such, Korhonen et al[2] showed that exposure to serologically confirmed acute enterovirus during pregnancy was inversely associated with atopic outcome in the offspring; this was not the case for acute influenza A or *Mycoplasma pneumonia*. Preconception use of maternal folic acid supplement and higher vitamin B12 concentrations at birth was reported to affect childhood lung function depending on MTHFR-C677T carriership.[3] There is also a growing interest in the association between grandparental exposure and asthma or allergic disease in the grandchild. Lodge et al[4] studied the link between grandmaternal smoking during pregnancy and grandchild use of asthma medications in a Swedish register-based study and found that children aged 1-6 years had an increased asthma risk if their grandmothers had smoked during pregnancy, independent of maternal smoking. This finding may support possible epigenetic transmission of risk from environmental exposures in previous generations. Finally, birth order has previously been shown to have an effect on the allergic disease.[5] Nevertheless, there is a need to carefully interpret potential causal effects and to take genetic and environmental confounding as well as residual confounding into account.[6,7] Consequently, systematic reviews and meta-analysis are very powerful and Flanigan's elegant review on prenatal maternal psychosocial stress and offspring's asthma and allergic disease in this year's Clinical and Experimental Allergy addressed causality very well.[8] Findings that atopic diseases and depression or anxiety tend to occur together in families indicate a genetic explanation for comorbidity, although this was not supported in a large twin study by Brew et al.[9]

There may also be factors that modify the association between a risk factor and subsequent asthma or allergic disease. Reports from Isle of Wight have suggested that breastfeeding duration may modify the effect of smoking during pregnancy on eczema from early childhood to adolescence,[10] and in a Finnish birth cohort, the association between pet exposure and sensitization was modified by pollen exposure in early pregnancy.[11]

1.2 | Big data

The definition, prevalence and time trends of outcomes such as asthma and allergic disease from early childhood to adolescence are also of great interest. Analysing "big data" allows data-driven methods such as hierarchical clustering and principal component analysis, which can be used to identify useful outcomes. Deliu et al[12] have used this approach to identify asthma subtypes that may further the understanding of asthma heterogeneity, exacerbations and severity. Time trends of food allergy from infancy to adolescence as well as transition of allergic sensitizations to common allergens as a prognostic factor for eczema, asthma and rhinitis are reported from the Isle of Wight cohort.[13,14]

1.3 | Postnatal exposures

Environmental exposure post-pregnancy has also been surveyed in Clinical and Experimental Allergy. Caillaud et al[15] report short-term effect of outdoor mould spore exposure on prescribed allergy medication sales in Central France. Quite unexpectedly, Brough et al[16] found that higher levels of environmental exposure to peanut in the first few months of life appeared to increase the probability of developing school-age peanut sensitization in atopic children.

Finally, Clinical and Experimental Allergy has also included reports on dietary pattern and respiratory pattern from nine European countries,[17] the influence of maternal and child's country of birth on the prevalence of parent-reported asthma, eczema and a diagnosis of anaphylaxis in Australia[18] and new interacting genes in eczema.[19]

2 | CLINICAL ALLERGY

2.1 | Component resolved diagnosis

We are increasingly using components to manage clinical allergy. Blankestijn et al[20] looked at whether Ara h 7 is useful in diagnosing peanut allergy. They compare it to Ara h 2 and Ara h 6 isoforms. Ara h 7, Ara h 2 and Ara h 6 had comparable utilities for diagnosing peanut allergy. Most individuals were co-sensitized to all three 2S albumins Ara h 2, 6 or 7 but some were only sensitized to one leading to the possibility of misdiagnosis when only one 2S albumin is used in a diagnostic algorithm.

Continuing on this theme, Geiselhart et al[21] had looked at whether component resolved diagnosis can help with buckwheat allergy. They identified a number of immunoreactive proteins from the crude buckwheat extract: Fag e 1 (legumin), Fag e 2 (2S albumin), Fag e 4 (hevein-like antimicrobial peptides) and Fag e 5 (vicilin-like). All four components showed better diagnostic precision than the extract-based ImmunoCAP.

Finally, Uotila et al[22] examined the IgE sensitization profiles in patient with different clinical responses to peanut and tree nuts in

a birch pollen area using the ISAC system. Specific IgE to Ara h 2 and Ara h 6 discriminated peanut allergic and tolerant participants. Only a minority of participants had species-specific sensitizations to tree nuts suggesting that many could potentially introduce them into their diet.[23]

2.2 | Chronic spontaneous urticaria

Chronic urticaria is a problematical condition for patients. Jörg et al[24] conducted a double-blind, randomized, placebo-controlled trial to assess the mode of action of omalizumab in these patients. Omalizumab therapy led to a significant reduction in FcεRI receptor density on basophils within a week persisting after the last injection. This contrasted with a lack of change in basophil activation testing suggesting that omalizumab's affect is cellular.

Continuing on the urticarial theme, Ruft et al[25] have developed and validated a disease-specific quality of life questionnaire for cholinergic urticaria (CholU-QoL). Such questionnaire is helpful to quantify condition specific issues for patients and may be helpful for clinical trials and improving routine patient management.

2.3 | Atopic dermatitis

Fieten et al[26] assessed whether the claim that Alpine climate therapy reduces the severity of atopic dermatitis. Using a pragmatic, open, randomized, controlled trial design, they enrolled children with difficult to treat atopic dermatitis. The interventions were 6-week personalized integrative multidisciplinary treatment period in the alpine climate or in moderate maritime climate. For up to 6 weeks after the Alpine intervention, atopic dermatitis was found to be better but this benefit was not maintained.

Another approach to allergen avoidance is the temperature-controlled laminar airflow device. Gore et al[27] have assessed it efficacy in severe atopic eczema in an open label, proof of concept study. Participants saw a clinically meaningful reduction in severity and an increase in quality of life over the 6-month intervention.

Continuing on the atopic dermatitis theme, a systematic review and a meta-analysis by Waidyatillake et al[28] suggested that the age of solid food introduction is not associated with the development of eczema.

2.4 | Food allergy

In the last year, we have seen evidence of the potentially severity of food allergy.[29,30] Many papers in 2018 focused on improving the management of food allergy.

Avoiding triggering allergens is the major challenge for patients with food allergy. Begen et al[31] looked at whether the 2014 European allergen information legislation had changed how consumers with food allergy behaved when eating out. Using both in-depth interviews and surveys with consumers with food allergy, they found a generally positive response with better availability of information and awareness of food allergy in eating out venues. The authors did though highlight continued inconsistencies in the implementation of the legislation.

Reier-Nilsen et al[32] assessed whether clinical or immunological factors are associated with the threshold for reactivity at double-blind, placebo-controlled food challenge in children with peanut allergy. They found that basophil activation, peanut skin prick test diameter and the ratio of peanut-specific IgE/total IgE were significantly associated with the threshold of reactivity and lowest observed adverse events level. Unfortunately, none of the factors were associated with severity. So we still lack predictive markers for the severity of allergic reactions.

Appel et al[33-35] looked for ways to improve the diagnostic approach for sesame allergy. Neither skin prick testing with commercial extracts nor basophil activation testing was perfect diagnostic tools but the authors suggested that they made be useful in parallel.

Lastly, the BSACI published guidance for the prevention of food allergy in children in 2018.[36] The guidance complemented the report from the UK's Scientific Advisory Committee on Nutrition (SACN) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). In summary, it recommended exclusive breastfeeding until around 6 months of life and introduction of age appropriate complementary foods from around 6 months of age alongside continued breastfeeding. However, the BSACI also recommended that where an infant was at higher risk of developing food allergy, parents may wish to start complementary foods (including egg and peanut) from 4 months of age in an age-appropriate manner to avoid risk of choking.

There is a constant effort to improve the effectiveness of oral immunotherapy for foods. Fauquert et al[37] tried to use peanut in sealed capsules to bypass the upper gastrointestinal tract ant potentially minimize adverse effects. In a randomized, double-blind and placebo-controlled trial design, they found similar mild oropharyngeal adverse effects in both arms but more frequent digestive and systematic adverse events in the peanut arm, so probably not a desirable approach.

2.5 | Drug allergy

Cabañas et al[38] looked at the value of the lymphocyte transformation test in drug reaction with eosinophilia and systemic symptoms (DRESS). In the recovery phase of DRESS, the lymphocyte transformation test had a sensitivity of 73% and specificity of 82%. This was much better than in the acute phase. This may be a helpful approach especially given that these patients cannot be challenged with the likely trigger(s).

Last year saw the publication of the Royal College of Anaesthetists 6th National Audit Project.[39,40] They describe the causes and investigation of peroperative anaphylaxis using a registry approach. The authors noted that harmonization of the approach to testing, access

to services, and MHRA reporting was needed. They noted that dynamic tryptase evaluation should be adopted with standardized clinic reports containing appropriate details of tests, conclusions, avoidance, cross-reactivity and suitable alternatives.

2.6 | Support groups

There is a limit to the support available from healthcare professionals. Jones et al[41] explored what motivates young people with allergies to engage with support groups using in-depth, semi-structured interviews. They reported very positive findings with reported improved self-esteem and confidence and improved adherence to self-management behaviours. We need to better signpost our patients to these support groups.

2.7 | Allergy in the elderly

Finally, Gray et al[42] published a case series of older people referred to an allergy clinic. While allergy was excluded in many cases, a number of new allergies were diagnosed leading to important changes in management. This is an overlooked population for allergist.

3 | ASTHMA AND RHINITIS

3.1 | Inducible laryngeal obstruction

In 2018, Lee et al[43] revisited the difficult associations and differences between vocal cord dysfunction (perhaps better called inducible laryngeal obstruction) and asthma in 69 consecutive patients attending a "difficult asthma service" that focuses on complex comorbidities. Their main objective was to compare a questionnaire approach to diagnosis of vocal cord dysfunction with direct vocal cord visualization during a mannitol challenge. In a detailed analysis, the authors confirm the frequent coexistence of asthma and cord dysfunction (~40%) and the inability to diagnose the condition with questionnaires.

3.2 | Asthma and pregnancy

It was always taught that asthma in pregnancy could be considered in thirds—a third remain unchanged, a third deteriorate and a third improve, which seems to be born out in observational studies.[44] Further, pre-pregnancy severity predicts pregnancy exacerbations.[45] In a study from Ali et al[46] take a further step and show that for mothers whose asthma is stable at enrolment and who have no history of severe exacerbations or current controller therapy are extremely unlikely to have an exacerbation during pregnancy and may therefore not require asthma surveillance.

3.3 | Triggers of asthma attacks

Looi et al[47] have thrown some light on why Rhinovirus (RV) infections might lead to more severe asthma. They examined the effects of RV on tight junction-associated proteins on airway epithelial cells (AEC) from asthmatic and non-asthmatic children. The AECs of children with asthma showed upregulation of mRNA for tight junction proteins but lower levels of these proteins compared to non-asthmatics. Infection of the cells with RV showed reductions in these proteins in all children though the effect was prolonged in asthmatic AECs. In addition, epithelial resistance was lower in asthmatic children and decreased further following RV infection. Thus, tight junction and epithelial dysfunction amplified by RV may be one mechanism by which RV infection induces asthma.

Personal air pollution monitoring is still in its infancy but likely set to move into the mainstream with improved response times and precision and provide new insights into associations with respiratory disease. Additionally, such monitoring can now be linked to wearable applications that document physical activity, respiratory rate and a host of physiological data. In a small study of patients with asthma, personal air pollution exposure did not seem to be associated with asthma control or lung function.[48]

3.4 | Underlying pathophysiology

A study by Periyalil et al[49] looks at pro- (M1) and anti-inflammatory macrophages (M2) in visceral and subcutaneous fat in obese asthmatic and non-asthmatic subjects undergoing bariatric surgery. The key findings relate to the increased M1 macrophages in visceral fat in obese asthmatics compared to non-asthmatics and a higher ratio of M1 to M2 in more severe asthma with positive correlations between macrophage types, lung function and markers of systemic inflammation. The study suggests at least one cellular component that might link obesity, inflammation and asthma that are clearly worthy of further study.

Meanwhile, Hastie et al[50] somewhat boldly attempted to try to disentangle a wide range of sputum cytokines and chemokines in relation to asthma severity. Additionally, they looked at the asthma severity and the various cytokines using factor analysis. The factor analysis was able to identify ten factors that grouped at least two cytokines per group and two groups that contained at least 16 common cytokines. But strikingly there were multiple overlapping inflammatory pathways identified across the whole spectrum of asthma severity suggesting that at the level of inflammatory proteins, the picture is complex, and therefore, specific cytokine biomarkers or even interventions targeting specific cytokines are unlikely to be successful in severe asthma.

The Mogensen et al[51] used 3 years of NHANES data to tease out the combined and separate elevated type 2 asthma markers, FeNO and blood eosinophils with asthma outcomes. When both markers were elevated, lung function was reduced and more severe asthma

reported. Elevated blood eosinophils alone were associated with more exacerbations and exacerbations of greater severity. The most important corollary of these findings would seem to be that across a broad spectrum of asthma severity both biomarkers are required to define current and future outcomes.

In a small group of preschool children, with severe recurrent wheezing who were bronchoscoped, Lezmi et al[52] evaluated the early airway pathology in relation to school-age asthma severity. Not surprisingly most children went on to have persistent asthma in later childhood and the severity and frequency of exacerbations correlated positively with submucosal eosinophil counts and lung function correlated positively with neutrophil counts, possibly related to ICS treatment. As in many studies, the more eosinophils the worse the asthma.

The Pentraxin family of ancient, conserved soluble proteins which include CRP, play an important role in recognizing foreign and altered self antigens. In a study by Gao et al,[53] members of the family were measured as potential markers of eosinophilic and non-eosinophilic asthma. Of the various pentraxins measured, pentraxin 3 in sputum showed the best predictive value for non-eosinophilic asthma with an AUC of 0.78.

3.5 | Phenotype specific therapy

In an open study of inhaled corticosteroid (ICS) withdrawal amongst 36 non-eosinophilic adult asthmatics, two thirds were able to stop ICS or reduce the dose.[54] In those who were able to stop, asthma control significantly improved following cessation. Predictors of failure were age and a higher eosinophil count, suggesting that perhaps those unable to stop or reduce in fact had an important eosinophilic component masked by their ICS. The study suggests that true non-eosinophilic asthma does not benefit from ICS.

3.6 | Impact of asthma

Hiles et al published a useful, if small, web-based database of adults with severe asthma.[55] Poorer asthma control generally was associated with absenteeism and self-reported impairment at work, while severe asthma per se at baseline was only associated with impairment at work. An important message here is that when exploring workplace issues associated with asthma, absenteeism alone is a poor measure and details of workplace engagement are as important as absenteeism in determining the effect of more severe asthma.

3.7 | Predicting future asthma attacks

Trying to predict future asthma exacerbations amongst severe asthmatics has been of obvious research interest. In a study by Kimura et al,[56] an adult cohort of severe asthmatics was reviewed regularly over 3 years. FeNO was the single most useful predictor of exacerbations after controlling for prior history of exacerbations, this being an obviously strong predictor of future exacerbations. The subjects in this study were generally good medication compliers with 30% on systemic corticosteroids. The report is interim as the authors plan to study the cohort for a further 3 years.

H_2S has recently been shown to be an important gaseous signalling molecule involved in modulating airway and vascular smooth muscle. In this study of asthmatics of varying severity, healthy subjects' serum and sputum H_2S have been examined.[57] Serum levels were lower and sputum levels higher in those with frequent exacerbations compared to those with fewer and elevated sputum H_2S predicted future exacerbations. Thus, a higher ratio of sputum to serum H_2S seems to predict more exacerbations though it is entirely unclear why H_2S should behave in this way.

3.8 | Long-term outcomes of asthma

In a study by Blackman et al,[58] 49 of 100 children hospitalized with severe wheezing before 24 months were followed up in early adulthood. When compared to controls, all were more likely to report current asthma. Those with RV or respiratory syncytial virus (RSV) were more likely have larger responses to bronchodilators but no significant differences in baseline lung function. Interestingly, RV early wheezers had higher FeNO than controls or RSV wheezers suggesting a stronger association between RV and subsequent allergic asthma.

3.9 | Asthma and food allergy

In this study by Patelis et al,[59] sensitization to food allergens amongst asthmatic adults was associated with higher levels of type 2 markers (FeNO, ECP, periostin and urinary eosinophil-derived neurotoxin) than asthmatics sensitized to aeroallergens only. Specific food sensitizations were associated with specific patterns of elevated type 2 markers especially periostin suggesting perhaps that food allergen sensitivity is more strongly associated with systemic type 2 inflammation than previously suggested. Of interest would be the associations in those with food allergy and in children with food sensitivities.

There is an interrelationship between asthma and food allergy which Bonner et al[60] describe. Many patients have both. Allergies to foods have been associated with severe asthma exacerbations while asthma seems to be a risk factor for life-threatening food induced anaphylaxis.

4 | ALLERGENS

4.1 | Novel allergens

A number of authors have identified new, clinically relevant allergens. Ruethers et al[61] have demonstrate that parvalbumin is the

major fish allergen in Asia-Pacific fish species and found a novel allergen called Ras k 1 in Indian mackerel.

Soongrung et al[62] have worked on the house dust mite species *Blomia tropicalis*, an important cause of allergic diseases in tropical and subtropical regions. They identified Blo t 7 as an important *B tropicalis* allergen that stimulates the TLR2 signalling pathways in AEC.

Novel allergens have also been identified for orange,[63] donkey's milk[64] and soya[65] in 2018.

4.2 | Variation in allergens

Dölle et al[66] looked at celery stalks and celeriac roots. They found that different cultivars of celery had different levels of the major allergen Api g 1. This is likely to explain the different allergenicity of different cultivars.

4.3 | Linking structure to allergenicity

Prodic et al[67] examined the stability of peanut allergens in the stomach. Ara h 2 and Ara h 6 remained mostly intact. This would preserve their allergenic capacity explaining their role in allergic reactions to peanuts. Hayen et al[68] have also looked at these two peanut allergens assessing the allergenicity of different isoforms.

Continuing with nut allergens, Blankestijn et al[69] looked at whether sensitization to Jug r 4 might explain why Jug r 1, 2 and 3 do not explain all cases of walnut allergy. Although the walnut 11S globulin Jug r 4 turned out to be a minor allergen, it had a very high positive predictive value for walnut allergy.

For food allergen components, we know that there is usually a relationship between the component to which an individual is sensitized and the presenting clinical symptoms. Park et al[70] looked to see whether there is a similar relationship with the *Dermatophagoides farina* allergens. Participants with rhinitis and/or asthma were mainly sensitized to the major allergens Der f 1 and Der f 2, whereas those with atopic dermatitis were sensitized to these major components plus one or more minor allergen component (eg, Der f 11, Der f 13, Der f 14, Der f 32 and Der f Alt a 10). This begs the chick or egg question: does this difference in sensitization patterns drive the different expressions of different allergic diseases or are the different allergic diseases responsible for the development of different sensitization patterns?

Allergen sensitizations does not always have a clinical significance. Stoevesandt et al[71] look at the sensitization profile of 490 dermatology patients without a history of sting-induced anaphylactic reactions. Many had sensitization to each of the wasp and bee components despite having no clinical history of a reaction.

Cross-reactivity is an important concept for allergens. Cantillo et al[72] have looked at cross-reactivity between tropomyosins in mosquito and house dust mite at humoral and cellular levels. They found both humoral and cellular cross-reactivity improving our understanding of these allergens.

4.4 | The matrix

We know that the allergen matrix can have an important impact on allergenicity. Pettersson et al[73] looked at whether a high or low fat content food matrix would affect allergic reactions to peanut. The high-fat recipe was associated with significantly worse reactions although the eliciting dose was similar.

5 | CONCLUSIONS

The year 2018 provided further advances in the field of allergy.[74] We look forward to publishing more interesting observations in 2020.

ACKNOWLEDGEMENTS

We would like to acknowledge the assistance of Catherine Hyland in putting together this review.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Roberts G, Almqvist C, Boyle R, et al. Developments in the field of clinical allergy in 2018 through the eyes of Clinical and Experimental Allergy, Part II. *Clin Exp Allergy*. 2019;49:1550–1557. https://doi.org/10.1111/cea.13535