Developments allergy in 2019 through the eyes of Clinical and Experimental Allergy, Part II clinical allergy

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Abstract

In the second of two linked articles, we describe the development in clinical as described by Clinical & Experimental Allergy and other journals in 2019. Epidemiology, clinical allergy, asthma and rhinitis are all covered.

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Epidemiology

Pet ownership and asthma

During 2019, there have been several highly interesting publications within the area of clinical and respiratory epidemiology focusing on asthma and allergies. Risk and benefits of pet ownership has been discussed for many years and although dogs have gained a huge upswing during the 2020 covid-19 pandemic, their role for primary and secondary prevention of childhood asthma and allergic disease is still under debate.

In adults, the sensitisation patterns to furry animal allergen components was recently characterized, and Fel d 1 and Can f 5 were found to be the most common cat and dog components sensitisation [1]. Also, mono-sensitisation was more common than poly-sensitisation and found to be an important predictor of asthma severity with increased blood eosinophils, fractional exhaled nitric oxide and airway hyperreactivity [2]. This aligns well with other data on molecular allergy diagnostics to refine characterisation of sensitisation [3] and basophil activation testing in the diagnosis of dog allergy in children [4]. The importance of timing of exposure to pets and dampness or mould on asthma and sensitisation in adolescence has also been reported in this year's Clinical and Experimental Allergy [5]. Findings were that different timing of pet and

dampness or mould exposure was not associated with asthma, but lower risk of sensitisation in adolescence was suggested, which could be partly attributable to reversed causation.

Other inhalant allergens of importance for sensitisation and asthma exacerbations are of course house dust mites (HDM). Novel findings from a Northern European population-based study shows that allergic sensitisation to storage mites are as common as HDM sensitisation and also associated with respiratory symptoms and asthma [6]. This indicates that storage mite sensitisation should be evaluated with regard to inclusion into the common inhalant allergen panel in Northern Europe.

Asthma co-morbidities

Comorbidities between asthma and neuropsychiatric disorders, especially attention deficit hyperactivity disorder (ADHD), has gained much attention in the last few years [7]. During 2019, Clinical and Experimental Allergy published papers on how atopic dermatitis or asthma are associated with child behaviour [8] and how parental asthma is related to offspring autism spectrum disorders, including the role of shared familial factors [9]. As such, having asthma or allergic disease could possibly negatively impact academic achievement in childhood which has been examined in two recent population-based studies [10, 11]. None of them found any association in younger children however in adolescents, there were remaining associations in sibling comparisons between uncontrolled asthma in Grade 9 and school performance which would be consistent with a causal association [11]. This information is of importance to clinicians when talking with children and parents about the implications of living with asthma or atopic disease.

Early life exposures as risk factors for allergy

Other important early life exposures that may have an impact on asthma and allergic disease include exposure to diet and microbiota. In a report from two iFAAM workshops, the role of dietary strategies to prevent childhood food allergy was summarised [12] and Mensink-Bout reported on the association between maternal and neonatal 25-hydroxyvitamin D concentrations and school-age lung function, asthma and allergy from the Generation R Study [13]. Helminth exposure however does not seem to be important for the difference in allergy-related outcomes between rural and urban communities [14] and the association between season of birth, childhood asthma and allergy to be mediated by lower respiratory infections [15].

Genetic risk factors for allergy

Finally, new genetic finding include sex-moderated interactions between IL4/IL13 pathway genes and prenatal environment on cord blood IgE levels [16] and a most interesting genome-wide interaction study of early-life smoking exposure on time-to-asthma onset in childhood [17]. Here, novel candidate genes interacting with early life tobacco smoke exposure and time-to-asthma onset in childhood were identified. These genes have plausible biological relevance related to tobacco smoke exposure. Further epigenetic and functional studies are needed to confirm these findings and to shed light on the underlying mechanisms.

Clinical allergy

Atopic dermatitis and other cutaneous manifestations

It can be very easy to diagnosis atopic dermatitis (or eczema) but there are important differential diagnoses that we need to consider. Mortz and colleagues took us through these in a well-illustrated paper in 2019 [18]. In another Danish paper, Thyssen and colleagues followed a group of 13,628 children and adolescents with atopic dermatitis for more than 10 years [19]. Two-thirds still had atopic dermatitis at 10 years with around one-in-ten having persistent disease. Persistence was increasingly more likely with increasing strength and number of medications in previous years. Bakker and colleagues looked at predictors of severe atopic dermatitis in a slightly older group of patients [20]. They identified a group of eight serum biomarkers which appeared to identify these patients. If replicated, this may be an approach to spotting patients who need more aggressive therapy before they develop side effects of chronic atopic dermatitis.

Finally an important paper from Cataldi and colleagues on the use of high doses of second generation antihistamines in chronic spontaneous urticarial [21]. In the review they concluded that bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, mizolastine and rupatadine all have excellent safety profiles even when four times the licenced dosages are used. Importantly, they highlight the need to rule out other potential cardiotoxicity risk factors for such as the long QT syndrome, older age, cardiovascular disorders, hypokalaemia, hypomagnesemia or other drugs that prolong the QT time or inhibit sgAH metabolism.

Drug allergy

Chan and colleagues published a paper highlighting the important issue of chlorhexidine allergy [22]. Around on-in-ten patients and nurses on a dialysis unit had cutaneous sensitisation with a

significant minority having clinical allergy. Reactions to contrast agents are a real concern. Seta and colleagues reported about the use of a low-dose provocation and skin tests to manage patients with hypersensitivity to gadolinium-based contrast agents [23]. Lastly, Chiriac and colleagues have looked at the negative predictive value (NPV) of a negative drug provocation test to a betalactam antibiotic [24]. In a group of 950 patients the NPV was calculated to be 94.8% (95% confidence interval 92.1-96.8). Six patient described a further reaction with the hallmarks of anaphylaxis but interestingly, where they could be re-tested, the work up was again negative.

There are some circumstances where allergist do not consider it prudent to test. Desroche and colleagues looked at one example of this, drug reaction with eosinophilia and systemic symptoms (DRESS) [25]. Here it may not be possible to identify the exact trigger meaning patients may have to avoid many potentially helpful medications. Desroche and colleagues used a caution provocation approach to test 91 drugs in 33 patients – 79 were tolerated with 9 patients having further DRESS or probable DRESS reactions, none serious. The paper has sparked some interesting discussion [26,27].

Anaphylaxis

The supply of Pharmalgen for bee and wasp venom testing stopped in 2019. Nassar and colleagues describe how to change patients to the Alutard SQ Bee and Wasp Venom products [28]. These have the advantage of having four different dilutions for updosing but they are not compatible for a rush or ultra-rush updoing strategy. There are alternative products that Erlewyn-Lajeunesse and colleagues have highlighted [29]. Sometimes the trigger for anaphylaxis cannot be identified. Bilo and colleagues reviewed idiopathic anaphylaxis in 2019 [30]. They highlighted that our lack of understanding of the pathophysiology although there is evidence of mast cell activation, the key differential diagnoses and approaches to long term management. A number of anaphylaxis guidelines have been published over the last 5-10 years [31,32]. There still seems to be knowledge gaps amongst healthcare professionals. Lejeune and colleagues reported that only a quarter of French emergency physicians would give a child experiencing anaphylaxis intramuscular adrenaline [33]. Finally, the impact of anaphylaxis on the patient needs to be considered. In a detailed qualitative study, Knibb and colleagues described four themes associated with anaphylaxis: the journey from fear to frustration; the need to maintain a healthy identity; control over uncertainty; and the supportive role of others [34]. These go some way to explain the negative impact of anaphylaxis on health related quality of life.

Food allergy: prevention and management

There have been large advances in our understanding of how to prevent food allergy. These are summarised in two paper. The first from Roberts and colleagues summarised two iFAAM workshop, the large EU project that has done much to advance our management of food allergy [35]. The second is a systematic review from Burgess and colleagues [36]. Their synthesis of the randomised controlled trial data indicated that introducing egg from 4 to 6 months and peanut from 4 to 11 months reduced the risk of egg and peanut allergy respectively.

In the drive to reduce the need for food challenge, Ruinemans-Koerts and colleagues examined the ability of basophil activation testing (BAT) to diagnosis milk allergy in young children [37]. BAT had a sensitivity and specificity of 100% (95% confidence intervals 86%-100% and 68%-100%, respectively) in IgE-sensitized children (41% of the tested children). Not surprisingly, the non-IgE-sensitized children all had a negative BAT with most, but not all, having a negative food challenge. So BAT may be helpful in investigating IgE-sensitised milk allergy. Continuing the theme of testing, Barni and colleague have assessed a modified food challenge protocol for children with food protein-induced enterocolitis syndrome (FPIES) [38]. Initial 25% of the full dose (five-fold lower with severe reactions) is administered with the remaining dose four hours later with a further 4 hour observation period. They assess their approach in 54 challenge and claim that it is safer than the alternative approaches to assessment patients with possible FPIES.

Further work from the iFAAM consortium has focused on precautionary labelling. Problems with this explain much of the poor quality of life associated with food allergy [39]. In a survey of 1560 consumer with food allergies, DunnGalvin and colleagues found that consumers wanted to know the process that companies had used to decide on the need for a precautionary label; they also wanted to see a statement and a symbol on the label to indicate that a quantitative risk assessment had been undertaken [40,41]. In a further paper, the group review the literature in this area [42]. They also went on to describe a basis for the development of more informative and transparent labelling, using quantitative risk assessment, that could improve consumers' well-being.

A quantitative risk assessment can only be undertaken if the population threshold for reaction is known. Elegbede and colleagues have generated threshold curves for peanut using data from the Mirabel survey [43]. In 204 children and young adults with a positive food challenge, 1% where found to react with objective symptoms was 0.26 [0.03; 2.24] mg of peanut protein (ED01). The

threshold was significantly lower in girls, with larger skin prick and Ara h 2 results. Threshold for individual patients can though vary, especially in the presence of a cofactor. However Versluis and colleagues reported that one or more potential cofactor was present in three-quarters of 153 reactions in 157 patients but these were not related to the severity of the reaction [44] suggesting that these potential cofactors often have no impact on the severity of an allergic reaction.

Ball and Luyt described the use of a milk ladder to introduce milk into the diet of pre-school children with IgE-mediated milk allergy [45]. Their criteria for this approach was skin and/or gastrointestinal symptoms only plus a skin prick test < 8 mm. They commenced with low-dose ingestion of a commercial baked milk biscuit with slow gradual increased exposure. In a total of 86 children, none experienced anaphylaxis and only eight patients were not tolerating almost all dairy products after four reviews. This approach would markedly reduce the need for hospital milk challenges.

Lastly, Brandström examined the individualizing omalizumab treatment using CD-sens could be an effective treatment for peanut allergy [46]. CD-sens is the lowest allergen dose that triggers basophils *in vitro*. If the CD-sens was not suppressed, a higher dose of omalizumab was given. At the trial endpoint, the 23 participants only had mild objective reactions at worse.

Patient pathways in allergy

Health services continue to evolve and it is important to listen to patients' and caregivers' experiences. In a qualitative study, Diwakar and colleagues have looked at 18 parents' experiences with paediatric allergy pathways in the West Midlands [47]. Many issues were raised by the parents including problems accessing health care, difficulties with being taken seriously by doctors and a lack of information about allergies. These need to be addressed when services are being recommissioned. One approach is to upskill primary care. El-Shanawany and colleagues presented a service evaluation of London's Whittington Hospital general practitioner with Special Interest community paediatric allergy clinic [48]. This ran alongside a pre-existing hospital clinics and was designed to increase the accessibility and provision of allergy. The new community service reduced waiting times while patient satisfaction with the hospital and community clinics was very high. This looks to be a practical way forward to improve the accessibility of allergy services.

Finally, Zijlstra and colleagues have looked at a very different approach to managing outpatients [49]. They assessed whether shared medical appointments might be an effective approach for 140 children and adolescents with atopic dermatitis in a randomised controlled trial.
After two months, there were no differences between in effects on emotional coping, quality of life, anxiety about corticosteroids and disease activity although both groups showed substantial improvements. This would be a very radical change to our current approach to outpatients.

Asthma and allergic rhinitis

Biomarkers and mechanisms of disease

Although the critical role of epithelial cell function in determining asthma pathophysiology and immune responses is recognized [50], to date, little attention has been paid to epithelial cells present in induced sputum. In the manuscript by Qin and colleagues, columnar epithelial cells in induced sputum were related to clinical features and characterized phenotypically and functionally using flow cytometry, qPCR and microarray [51]. There was a relationship between sputum columnar epithelial cell numbers and male gender, severe asthma and type 2 asthma. Specifically, a gene signature which aligned with CCLA1 mRNA and periostin protein, both of which have previously been associated with IL-13 mediated disease, were elevated in patients with "columnar epithelial cell high" sputum in the presence of eosinophilia. This manuscript highlights the value of using viable epithelial cells in sputum as non-invasive biomarkers to define asthma phenotype and potentially may aid in identifying suitable add-on therapies for patients.

Although B cell function is essential in allergic diseases, relatively little is known about the role of recently described B regulatory cells in patients with asthma. Wiest and colleagues investigated Breg cells in adults with allergic asthma, with specific focus on their frequency and expression of the regulatory cytokine, IL-10 [52]. Both the frequency of peripheral blood Breg cell subtypes and their ability to secrete IL-10 was altered in patients with asthma, and treatment with oral steroids differentially affected IL-10 secretion in specific Breg populations. This highlights the differential role of Breg subsets in patients with asthma and suggests their role in individual patients may determine degree of response to oral steroids resulting from IL-10 secretion.

The utility of blood eosinophils to determine eligibility for biologics as add-on treatments for patients with severe asthma has largely been determined from a single measurement undertaken in clinical trials. However, little is known about the longitudinal variation in blood eosinophils in

patients and their utility as a biomarker from a pragmatic real-world clinic. Rakowski and colleagues have addressed this very important issue by reviewing variability in blood eosinophils measured over a 5 year period [53]. Only 13/219 patients had a blood eosinophil count consistently above 300 cells/mcl. Half of patients had a fluctuating blood eosinophil count that intermittently rose above 300 cells/mcl and the remaining 46% never had a level above 300 cell/mcl. This highlights the need for repeated blood eosinophil counts to be undertaken in the same patient over time to understand individual trajectories and determine optimal therapeutic interventions with biologics for the individual.

Biomarkers that predict either the severity of a current asthma exacerbation, or of future exacerbations would clinically be extremely useful, but little is currently available, other than the repeated finding that a recent severe exacerbation means a high risk of a further exacerbation in the next 4 weeks [54]. Although a retrospective review, the study by Yii and colleagues related blood eosinophils on admission during a life-threatening asthma attack, to clinical parameters such as arterial blood gases and duration of mechanical ventilation [55]. The acute blood eosinophil count on admission did not relate to outcome for the acute admission. However, an admission eosinophil count of >1.2x109/L was associated with a higher risk of future emergency visits or hospitalisations for asthma during a median follow-up of 52 months. This study suggests a high blood eosinophil count at presentation with a severe, life-threatening episode of asthma should raise even greater concerns and need for close follow-up to prevent future repeated severe presentations.

Murine experimental models of rhinovirus induced exacerbation of asthma are a challenge to develop, thus our understanding of the mechanisms underlying acute asthma exacerbations has been very limited to date [56]. As a means to overcome the limitations of mechanistic studies, increasingly, in vivo virus challenge studies are being undertaken in adults [57]. Infection with rhinovirus-16 was used in such a manner in adults with mild to moderate asthma by Ravi A and colleagues [58]. Transcriptional gene profiling by RNA sequencing of nasal epithelial cells was examined 7 days prior to experimental infection with rhinovirus 16 and compared to 3, 6 and 14 days after infection. Patients could be split, according to their interferon alpha and gamma response genes into 3 categories; early resolvers, who had cleared virus by day 6 and had an increased interferon response at day 6, late resolvers, who cleared virus by day 14 and had increased interferon responses at days 3, 6 and 14 and finally non-resolvers, who had not cleared virus by day 14 and did not have an increase in interferon responses at any of the time points

assessed. Even though only 20 patients were included, and all had mild-moderate asthma, this study highlights the degree of heterogeneity between patients in response to a fixed dose rhinovirus infection and the need for biomarkers to identify individualised responses to enable prediction of the likely severity of exacerbations for each patient.

A biomarker that is now part of diagnostic guidelines for asthma in both children and adults is an elevated exhaled nitric oxide (FeNO) level [59]. However, there is evidence that FeNO may be elevated in healthy individuals without asthma, especially in those with atopy alone. Nerpin and colleagues have addressed this important issue by investigating factors that determine FeNO levels in healthy men and women without lung diseases [60]. FeNO values were significantly higher in men, and in older subjects (60-67 years, compared to those aged 39-48 years), it was also higher in taller subjects. Smoking resulted in 30% lower FeNO levels, while sensitisation to grass and perennial aeroallergens resulted in higher levels. Just as age-related reference values have been generated for children, these data suggest similar age and sex related reference ranges may be needed prior to interpreting values from adults older than 50 years.

An extension of FeNO is the use of alveolar NO. In searching for a model for the alveolar concentration of NO Sato and colleagues have explored various models and compared their predictions with iNOS mRNA expression in the airway and the associations of the various models lung function [61]. Interestingly the original two compartment model showed the only associations with iNOS mRNA expression in both proximal and distal airway.

In a study focused on polymorphism of a gene encoding the low affinity IgE receptor, CD23 (FCER2) was found to be associated with reduced FeNO levels in well controlled asthmatic children using ICS for asthma management [62]. The polymorphism in FCER2 was considered to lead to reduced expression of CD23 resulting in lower levels of IgE and reduced FeNO. However the findings might be confounded by the direct effects of ICS on lowering FeNO though in this study ICS dosage was not correlated with FeNO.

Kozlik and colleagues have reported a detailed and complex study of airway structure in ~100 asthmatics linking structure, cytokines, biomarkers and lung function in asthma [63]. The findings broadly suggest that remodelling is most closely associated with classic Th2 biomarkers together with systemic neutrophilia and a variety of other inflammatory markers. CT airway metrics in fixed

airway obstruction correlate with distal rather than proximal airways as suggested by physiological changes.

Finally Blais and colleagues have confirmed previous studies showing that airway hyperresponsiveness to mannitol is not influenced by extra deep inhalation though it is not possible to administer mannitol without deep inhalation so the effect may be masked, whereas these do protect against methacholine induced bronchospasm [64].

Prediction of asthma and asthma risk factors in children

Numerous childhood asthma prediction scores have been developed from birth cohorts around the world. The consistent limitation of each is their high positive predictive values, but low negative predictive values, making it difficult in the clinic to be able to say to parents that their child is unlikely to develop asthma. A further asthma prediction tool has been reported from the Manchester Asthma and Allergy Study (MAAS) by Wang and colleagues [65]. The predictive tool incorporates 5 risk factors; wheeze after exercise; wheeze causing breathlessness; cough on exertion; current eczema and skin prick test sensitisation. When applied at 3 years of age, a score of >3 identified children at high risk of developing asthma by school age, with a positive predictive value >75%. In contrast if a child had a score of 0 the risk of asthma at school age fell to PPV 9%. Although this is a predictive tool that can be easily used in the clinic, the limitation remains the number of children that would have a score of 0 attending a paediatric clinic at 3 years old. This is likely to be a very low number, so this score may be useful in primary care, or for community surveys, but may have limited application in a paediatric clinic setting.

The role of vitamin D supplementation in children in preventing asthma has yielded few positive results. However, increasing evidence is apparent of the beneficial role of antenatal maternal vitamin D status and protection from wheezing and asthma in offspring. A combined analysis of two trial has shown that vitamin D supplementation during pregnancy resulted in a significant reduced risk of asthma/recurrent wheeze in the offspring [66]. In addition, mothers with early and/or late vitamin D sufficiency had a lower risk of offspring with asthma or recurrent wheeze by age 3 years [67]. In the manuscript by Mirzakhani et al the role of both paternal and maternal asthma and cord blood vitamin D status on development of asthma and recurrent wheeze by age 3 years was investigated [68]. Highest risk was found in children with both parents with asthma and those whose mothers had poorly controlled asthma antenatally. Children whose mothers had vitamin D sufficiency during early and late pregnancy and also had cord blood vitamin D

sufficiency had a lower risk of wheeze / asthma development by age 3 years, suggesting an important role of maintaining maternal asthma control and vitamin D sufficiency throughout pregnancy to minimise asthma risk in the offspring.

Numerous large cohort studies have investigated risk factors for asthma in children, but a potential confounder from associations found is the role of reverse causation. Data from the ISAAC phase three study of 370,000 children in more than 3000 schools in 42 countries have been analysed by Silverwood and colleagues in order to address this issue [69]. Individual level exposure data and school level exposure data were analysed in order to explore the role of reverse causation in asthma associated risk factors. Using both types of analyses at age 6-7 years, current paracetamol use, early life antibiotic use and open fire cooking were associated with asthma. At age 13-14 years, strongest associations were seen with current paracetamol use, cooking on an open fire and maternal tobacco use, again using both types of analyses. The authors argue given the consistency in associations using both types of data, the likelihood of reverse causation explaining the findings is low. Additionally they suggest that the school level associations would be more useful for health policy development modifying lifestyle and environment.

The role of maternal diet, and a Mediterranean diet in protecting from childhood asthma has been extensively investigated [70,71]. The role in adult respiratory diseases has been less well studied. Cazzoletti and colleagues have investigated relationship between dietary fats, olive oil, asthma and allergic rhinitis [72]. High intake of monounsaturated fatty acids, oleic acid and olive oil were associated with a lower risk of current asthma, but the same diet was not associated with lower risk of rhinitis, suggesting different mechanisms underpinning immune responses arising in the lower airway from gut constituents, compared to upper airway allergic responses. There is also the question as to whether a change to such a diet might influence established asthma in any useful way.

Eczema is considered an important predictor of future asthma development in children. Data from the Cincinnati Childhood Allergy and Air Pollution prospective birth cohort identified two high-risk groups for asthma development [73]. A group with early eczema and food allergen sensitisation, and another without early eczema, but with multiple aeroallergen sensitisation. Further strength was added to these associations in children with the specific genetic risk allele KIF3A rs12186803. Although early and multiple aeroallergen sensitisation is recognised as high risk for future asthma, these data highlight the importance of assessing food allergen sensitisation, specifically in

children with early eczema to help identify a group that may be more likely to develop future asthma.

Asthma in disadvantaged populations and comorbidities

Poor asthma control and high-risk has been recognised in children from low and middle income backgrounds. Interventions to improve control in these populations can be challenging, especially if they involve attendance to a healthcare setting, since parents are usually working full time and unable to attend frequent appointments. School-based interventions are a potential solution to this problem and has been investigated by Marsland and colleagues [74]. A school based stress management and coping intervention was assessed in a pilot randomised trial of 104 low-income children. 71% of eligible children, mean age 10 years, participated, with an additional 12% drop-out rate. The intervention resulted in reduced symptoms of depression, perceived stress and child reported asthma symptoms. Perhaps surprisingly and somewhat disappointingly there was no difference in asthma control. However, the preliminary findings suggest further assessment of school based interventions may be useful as a means of targeting multiple psychological asthma related disparities.

The impact of mental health on asthma control and morbidity is recognised. However, there is little evidence that ties together mental health symptoms with objective markers of asthma control. Zhang and colleagues have reported the relationship between depressive symptoms associated airway inflammation and bronchodilator response [75]. 198 adults with asthma had induced sputum, blood tests and an assessment of symptoms of depression using the Hospital Anxiety and Depression Scale. The group with evidence of depression (n=24) had worse bronchodilator response and higher sputum neutrophils compared to those without depressive symptoms (n=174). Moreover, inflammatory mediators associated with neutrophilia (IL-1beta, TNF-alpha) were also increased and correlated with the depression score. These data suggest depression may be an objective factor contributing to more severe asthma.

The association between insomnia and asthma control and adults was investigated in a large Swedish cohort by Sundbom and colleagues [76]. Of 1272 participants with asthma, the prevalence of insomnia symptoms was significantly higher in those with uncontrolled asthma, compared to controlled or partially controlled symptoms. Importantly rates of insomnia were not different in those with controlled asthma compared to non-asthmatics. An assessment of sleep duration and improved sleep hygiene should be considered in poorly controlled asthma.

Tobias and colleagues looked at carotenoids and the n-6/n-3 PUFA ratio as dietary markers of fruit and vegetable and fat intake respectively [77]. The population was African American and Hispanic adolescents with asthma and obesity, together and separately and a group of normal weight non-asthmatic controls. The levels of total carotenoids positively associated and the n-6/n-3 ratio inversely correlated with predicted FEV1 only in the obese asthmatic group. The study supports other population studies where diets low in fruit and vegetables and high in saturated fats are associated with more asthma – in this study particularly obesity related asthma.

Lastly, on a slightly different note, Kansen and colleagues have looked at asthma triggers amongst children referred for secondary care the number of allergic and non-allergic asthma triggers were strongly associated with quality of life [78]. The study emphasises the importance of considering triggers and providing amelioration where possible. It also underlines the importance of knowing the atopic status of children and the importance of possible atopic triggers.

Response to therapies

The role of genetic influences and susceptibility in response to asthma therapies are well recognized, especially in the context of beta2-agonists. However, it is becoming increasingly apparent that ethnicity plays an important role when considering response to steroids. Hernandez-Pacheco and colleagues have undertaken a GWAS of response to inhaled corticosteroids in children from mixed ethnic backgrounds, focussing on Puerto Ricans and African Americans [79]. A meta-analysis of two GWAS of asthma exacerbations in children of mixed ethnic backgrounds (Hispanics/Latinos, African Americans) being treated with inhaled corticosteroids was undertaken. A novel genetic association APOBEC3B and APOBEC3C and poor response to inhaled corticosteroids was found and was replicated in European populations. This suggests future consideration may need to be given to identifying specific susceptibility genotypes of low steroid response in children, especially in those with severe exacerbation prone asthma, perhaps necessitating the earlier introduction of add-on biological therapies.

Another factor that may affect response to inhaled corticosteroids is DNA methylation. Epigenome-wide DNA methylation was assessed in children prescribed inhaled corticosteroids from three independent and ethnically diverse cohorts [80]. Differential DNA methylation of IL12B and CORT expression were associated with inhaled corticosteroid response in children with persistent asthma. Therefore, in addition to gene expression, it is apparent that pharmaco-

methylation also identified markers of treatment sensitivity in children with asthma, regardless of ethnicity.

Another factor that may determine efficacy of inhaled steroids is particle size. Extra-fine particles are thought to be associated with improved lung delivery and may therefore have improved response. Kuo and colleagues investigated change from fine to extra-fine particle inhaled corticosteroids (mass median aerodynamic diameter 1.1μm) on patient reported outcome measures in adults with asthma [81]. A switch from fine to extra-fine particle formulation in an equivalent dose (half the dose) was associated with an improvement in asthma control questionnaire and asthma quality of life questionnaire after 8 weeks, but there was no difference in lung function, FeNO or blood eosinophils after the change. Therefore, although subjective markers of asthma control improved, objective assessments of type 2 inflammation and lung function were unchanged. The important point would be to assess whether the subjective improvement is maintained over a longer period.

Air purifiers have been proposed as potential complementary additions to improving asthma control. However, their efficacy remains uncertain. It is likely that their role is influenced by the phenotype of the patients and their pattern and severity of allergen sensitisation. The role of the ALYATEC environmental exposure chamber has therefore been investigated by Gherasim and colleagues specifically for cat allergic asthmatics [82]. They undertook a randomised double-blind cross-over trial in 24 cat-allergic patients with mild GINA level 1 asthma. Participants were exposed to approximately natural levels of cat allergen and then randomised to active or placebo air cleaners. Active air cleaners resulted in a lower incidence of both early and late asthmatic response, compared to placebo. This suggests air cleaners may be most effective when they filter specific allergens, and this air filter may be especially useful in patients / families with asthma who are sensitised to cats, but reluctant to remove cats from the household.

Airway remodelling

Although airway remodelling is frequently quantified in studies, non-invasive clinical assessments that correlate with parameters of airway remodelling have been difficult to find. Alagha and colleagues have investigated the relationship between of the cough and sputum questionnaire (CASA-Q) and goblet cell hyperplasia in endobronchial biopsies from adult non-smokers with asthma [83]. Although the degree of goblet cell hyperplasia was related to neutrophilic inflammation in broncho-alveolar lavage, there was no relationship between the CASA-Q score

and goblet cell hyperplasia. So is goblet cell hyperplasia more of a feature of asthma/COPD overlap? There was a closer association between the questionnaire and airway eosinophils, rather than goblet cell hyperplasia. Thus, the search for clinical outcomes relating to this parameter of airway remodelling are still needed.

The relationships between pathological changes in different airway compartments (tissue and lumen) and less invasive sites, such as the blood or imaging remains a challenge and unmet need, since direct assessments of airway pathology require invasive tests. The relationships between endobronchial biopsies, broncho-alveolar lavage, blood, CT changes and lung function were investigated by Kozlik et al to try to address this issue [84]. 105 adults with asthma, of whom approximately half had evidence of fixed airflow obstruction were included. Patients with fixed airflow limitation had higher blood and BAL eosinophilia, increased serum fibrinogen, periostin and ADAM33, they also, as a group had higher blood neutrophils. A cluster analysis of CT scoring revealed 3 separate clusters determined by RBM thickness collagen I accumulation and inflammatory markers in the airways. Overall, the findings showed airway remodelling correlated best with Th2 immune parameters and blood neutrophilia, not so well with lung function. However, assessments of bronchial smooth muscle were not made in the biopsies, and that may be the better parameter to reflect lung function than airway wall thickness (from CT) or RBM thickness.

Severe asthma epidemiology

Although studies frequently quote that severe asthma affects between 2-5% of the whole population with asthma, it is difficult to find prevalence data that has used more recent definitions recommended by European / American Task Force groups. Backman and colleagues applied the definitions from the United States Severe Asthma Research Programme 2000, more recent ERS/ATS Task Force (2014) and GINA 2017 to a cohort of Swedish adults with asthma [85]. Prevalence using the 3 definitions was 3.6%, 4.8% and 6.1% respectively, and these patients represented approximately 0.5% of the general population.

Asthma COPD overlap syndrome

Obstructive lung diseases have proved difficult to pin down pathophysiologically with oscillating conceptions of the relationships between asthma and COPD. In a relatively large study with longitudinal follow up the Park and colleagues make a good case for the asthma/COPD overlap syndrome to be considered as an independent entity based on differences in severity and the

fixity of airway obstruction but without any evidence of a genetic component [86]. A key question arising is how this entity should be managed?

Allergic rhinitis

The role of digital technologies in improving management of common chronic conditions is an area of increasing interest. One of the biggest challenges clinicians face is encouraging patients to remember their maintenance therapy, even when they are well, to help maintain control. The utility of a mobile app to improve adherence to treatment for allergic rhinitis was investigated by Menditto E and colleagues as part of the MASK Study, being run in 22 countries [87]. Patients were assessed in their completing of a mobile diary app. Although a large number of patients had registered to use the app (>12,000), only 1,195 had registered data at any one time that could be included in the analysis. From the data that was available, at least 69% of patients were non-adherent to prescribed regular allergic rhinitis medications. The use of the digital technology has shown in a real world setting the low levels of adherence to prescribed therapy, and whether there is a need to investigate the efficacy of as required vs continuous treatments for allergic rhinitis.

In the context of allergen immunotherapy for allergic rhinitis, it is often difficult to know which patients will respond best to immunotherapy, especially if there may be evidence of sensitisation to multiple allergens. In the study by Zidarn et al the utility of the basophil activation test was assessed as a functional test to understand the importance of HDM sensitisation in patients with allergic rhinitis [88]. Specific IgE or IgG to HDM did not distinguish symptomatic and asymptomatic patients that were sensitised, but symptomatic patients had a tenfold lower threshold for in vitro basophil activation, symptomatic patients had sensitisation to a greater number of allergen components and a greater number of symptomatic patients were sensitised to Der p7 and Der p 23 than asymptomatic. The study has highlighted more specific tests that can be undertaken to understand the functional relevance of HDM sensitisation which may help to identify patients most likely to benefit from allergen immunotherapy for allergic rhinitis.

Although the role of neutrophils and their activation status in the lower airways has been linked to more severe asthma, to date, the role of neutrophils in influencing severity of chronic rhinosinusitis has not been studied. Hwang and colleagues investigated the presence of neutrophil extracellular traps (NETs) in nasal secretions from patients with chronic rhinosinusitis during stable disease and exacerbation [89]. The role of NETs in secreting chemokines and affecting nasal epithelial permeability was assessed. Although production of NETs was increased during exacerbations of

chronic rhinosinusitis, the chemokines secreted resulted in strengthened epithelial barrier function. Thus the functional role of NETs in chronic rhinosinusitis remains uncertain and neutrophilic infiltration during exacerbation may indeed be beneficial.

Conclusions

The year 2019 provided further advances in the clinica allergy. In the related paper we look at more mechanistic aspects [90]. We look forward to publishing more interesting observations in 2021.

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