

REVIEW ARTICLE

Asthma and allergic rhinitis in childhood: what's newCarla Mastroiilli^{1,2}, Daniela Posa², Francesca Cipriani³ & Carlo Caffarelli¹

¹Pediatric Clinic, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy; ²Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany; ³Pediatric Unit, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

To cite this article: Mastroiilli C, Posa D, Cipriani F, Caffarelli C. Asthma and allergic rhinitis in childhood: what's new. *Pediatr Allergy Immunol* 2016; **27**: 795–803.

Keywords

allergy; allergic rhinitis; asthma; childhood; diagnostics; management; pediatric; respiratory; risk factors; treatment

Correspondence

Carlo Caffarelli, Pediatric Clinic, Department of Clinical and Experimental Medicine, Azienda Ospedaliera-Universitaria, University of Parma, Via Gramsci 14, 43122, Parma, Italy telephone: +39 0521 702207 fax number: +39 0521 702830 E-mail: carlo.caffarelli@unipr.it

Accepted for publication 7 November 2016

DOI:10.1111/pai.12681

Abstract

Novel approaches are currently offered for the diagnostic workup and therapeutic management of allergic rhinitis and asthma. New predictive biomarkers of allergy and asthma are available. Primary and secondary prevention, earlier intervention, and modification of the natural history of allergic rhinitis and asthma are being intensively investigated. This review highlights advances in the understanding of the etiology, diagnosis, and management of atopic airway diseases in childhood, as well as prenatal and early-life risk factors and strategies for prevention.

Allergic disorders are the non-communicable diseases with the earliest onset (1). Their burden is growing, especially in the middle-income countries (2). Allergic rhinitis (AR) and asthma are also the most frequent chronic diseases in childhood (3). The social and economic costs of AR and asthma are impressive, as these diseases heavily influence the patients' social life, school performance, sleep quality, and psychosocial interactions (4). Recently, important advances have been reported in the field of respiratory atopic diseases in childhood (5, 6). This review focuses on recent scientific progress concerning genetic and environmental risk factors, preventive strategies, newest diagnostic tools, and therapeutic opportunities.

Epidemiology

Asthma and AR have increased in prevalence and incidence, starting from the 1960s in Western countries and later in middle-income countries. For example, in the Middle East the prevalence of AR ranges nowadays from 9% to 38% (7), probably due to an ongoing shift toward a 'Western' lifestyle. An increase in asthma incidence from 1992 to 2008 in Canada, ranging from 0.6 to 29.5 per 1000 persons (children and

adults), has been recently reported (8). In contrast, a study based on the ISAAC questionnaire showed that in Switzerland the incidence of asthma and AR has not further increased during the 21st century (9). Moreover, population-based studies show that in the last decade the incidence of asthma in childhood has declined in the Netherlands (10) and in England (11). However, the prevalence of current and lifetime AR is still on the increase (by 5.5% and 13%, respectively, from 2001 to 2012) in England (11).

Origins of asthma and allergic rhinitis**Genetic factors**

Genetic factors and *in utero* and after-birth environmental exposures lead to the increase in asthma and AR through altered immune and organ development and imbalance in innate and adaptive immunity (12). Heritability varies from 35% to 95% for asthma and from 33% to 91% for AR. The Multicentre Allergy Study (13) showed that in birth cohort children, parental allergy significantly increases the risk of allergic disease and triples that of allergic multimorbidity. Genomewide association studies have found a link of asthma

(14) and AR (15) with different chromosomal regions. Chan et al. (16) confirmed the association of single nucleotide polymorphisms (SNPs) in 17q21 locus as the most replicated asthma susceptibility region and, consequently, found five SNPs of the protein C gene (PROC) on 2q14 associated with asthma. Epigenetic processes may mediate environmental effects on gene expression, resulting in occurrence of atopic respiratory diseases. *In utero* environmental exposure, including smoking, air pollution, diet, medicine, microbes, infection, and season of birth, may influence the occurrence of atopic diseases through epigenetic mechanisms (12). Gene alterations can be also transmitted to the offspring. Asthma and AR comorbidity has been associated with a paternally transmitted DNA methylation within melatonin receptor-1A (MTNR1A) gene in the 4q35 linkage region (17).

Structural changes

Morphologic changes in the bronchial wall, known as 'remodeling', accompany symptoms of asthma. Initial changes leading to remodeling, including thickness of the basement membrane (BM), subepithelial deposition of laminin, and collagen IV in the BM, have been defined as starting at less than 4 years of age in asymptomatic children predisposed to asthma (18). Similar structural changes in bronchial mucosa have been described in children with asthma, cystic fibrosis, and primary ciliary dyskinesia (19). This might suggest a common feature of bronchial remodeling in chronic respiratory diseases.

Microbiome and infections

How environment predisposes to atopic respiratory diseases remains mostly unexplained. According to the 'hygiene hypothesis', microbial exposures in early childhood may prevent allergies and asthma by modulating the T helper type cell Th1/Th2 and Treg imbalance. Along this line, it has been demonstrated that consumption of farm dairy and living in a traditional farm environment with domestic animals protect children from atopy (20). In this context, human microbiome may play an important role by activating the maturation of the host immune system. Accordingly, in pregnancy, maternal antibiotic use and urinary tract infections are linked with higher risk of childhood asthma (21). Furthermore, exposure to microbes *in utero* due to respiratory viral infections in pregnant women with asthma is associated with higher frequency of wheezing in their infants (22). Cesarean sections (CS) modify the microbiome composition in early postnatal life and increase the risk of asthma (21). Among children with parental history of asthma nested in a birth cohort evaluated at 6 years of age, CS is associated with AR onset (23). Nevertheless, a meta-analysis has not demonstrated a significant increase in the risk of AR among children born by CS (24). In infancy, the risk of developing asthma is enhanced by microbiome-modifying factors, such as antibiotic use, daycare attendance, and fewer older siblings (21). Asthma development is often preceded by viral bronchiolitis and wheezing, in up to 90% of cases among younger children (25), particularly by rhinovirus infections (26). Allergic heredity, increased severity

of wheeze, and atopic eczema were risk factors for asthma at school age among infant wheezers (27). The other side of the coin is that children with parental atopy, eczema, and wheezing are more prone to present prolonged/recurrent rhinitis (at least 4 weeks) in the first 18 months of life (28). Interestingly, immigrants have been shown to undergo a permanent change in microbiome exposure. Ethnic background interferes on the prevalence of asthma among no-Japanese Brazilian (NJB) and Japanese Brazilian (JB, born in Brazil from Japanese families) schoolchildren (29), showing a higher prevalence in NJB than in JB. Conversely, a multicenter cross-sectional study did not show differences in prevalence of AR and sensitization of grass pollen between immigrant children born in Italy vs. Italians (30).

Diet and vitamin D

It has been observed that changes in maternal and/or infant diet, particularly vitamin intake, Mediterranean diet, timing and diversity of infant feeding (31), can influence the risk of allergy and asthma in childhood (32). Several trials examined participants with familial or personal allergy risk. Interest is increasing in understanding whether results can be applied across a general population and the possible time window of diet effect. Patel et al. found that Western diet pattern (high fat content, processed foods) was significantly associated with asthma. No association between traditional diet (mixed meat, fish, fruit, and vegetables), other diet (predominantly grains and nuts), and allergic sensitization was detected (33). Vitamin D is related to maturation of the lungs and immune system. Low serum levels of vitamin D may be associated with respiratory infections, lung inflammation, bronchial hyper-responsiveness (BHR), poor asthma control, reduced response to steroids, severity of asthmatic symptoms, and increased asthma/allergic disease incidence (34, 35). A correlation between vitamin D deficiency and AR with suppressive effect on nasal mucosa inflammation has been proposed (36). A direct association in the development of AR between vitamin D deficit and male gender was illustrated in HUNT study, with the opposite effect in females (37). Possibly, the relationship between AR and vitamin D deficit might depend on the deficit severity (38). Additionally, vitamin D intake during pregnancy is negatively associated with risk of both asthma and AR (39). However, interventional studies have shown an insufficient evidence to support prenatal maternal vitamin D supplementation for preventing recurrent wheezing, asthma, and AR (40, 41).

Allergen sensitization

Aeroallergen sensitization is a risk factor for childhood AR and asthma. However, its value regarding early asthma prognosis is limited, as it develops later in childhood (42). In hospitalized first-time wheezing children, sensitization was found as a risk factor for persistent asthma (43). In a population-based birth cohort (42), sensitization to foods is more common than to aeroallergens until 5 years of age, while sensitization to aeroallergens increases later in childhood and adolescence, with a peak at 10 years of age in asthmatics and

26 years in AR patients. In a large Italian cross-sectional study, children affected by pollen-related AR were very frequently polysensitized (84.9% of them were sensitized to at least three pollen extracts) (44). Early polysensitization can predict allergic multimorbidity in childhood (45). Polysensitization, comorbidity, and/or cross-reactivity toward mammalian animal allergens are prevalent in patients with asthma (46) and AR (44) and are associated with severe allergic disease. The availability of allergen molecules from several protein families has advanced our understanding of IgE-mediated responses and enabled 'component-resolved diagnosis' (CRD), helping clinical practitioners to improve the diagnostic algorithm (47).

Diagnosis and management

Phenotypes and endotypes of allergic rhinitis

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification (48), AR was defined as mild when there was no impairment of Health-Related Quality of Life (HRQoL) items (sleep, daily activities, work/school performance, troublesome symptoms), and moderate/severe when items were compromised. This classification was recently validated in a Spanish pediatric population and used to discriminate severity grades for ages 6–12 years (49). Furthermore, Valero et al. (50) categorized the original four HRQoL items with different levels of severity: mild (no affected items), moderate (1–3 affected items), and severe (all affected items). This modified ARIA classification has been validated as more precise in discriminating moderate–severe AR among untreated pediatric patients (51). Several phenotypes of rhinitis (52) and asthma have been proposed, facilitating disease classification by clinicians. Kurukulaaratchy et al. (53) described four rhinitis phenotypes among 18-year-old patients: moderate childhood-onset rhinitis, mild adolescent-onset female rhinitis, severe earliest-onset rhinitis with asthma, and moderate childhood-onset male rhinitis with asthma. Consequently, atopy was a marker of increased disease severity; more severe rhinitis and earlier onset were associated with asthma. 'Local allergic rhinitis' (LAR) is a phenotype characterized by nasal Th2 allergic inflammatory response with local production of specific IgE (sIgE). It has been identified in cases of positive response to nasal provocation test and/or detection of sIgE in the nasal mucosa without evidence of systemic atopy. LAR is defined as either the initial, transient stage in the natural history of AR, or as a stable phenotype never evolving to 'systemic' IgE sensitization (54). Novel diagnostic biomarkers such as nasal detection of interleukin-5 (IL-5) and thymic stromal lymphopoietin (TSLP) offer relevant insights concerning LAR (55).

Phenotypes and endotypes of asthma

Classifications of asthma phenotypes have been performed in children cohorts by multivariate and unsupervised analyses (56). Age at onset, BHR, treatment control, and multiple sensitizations were the most important parameters to define asthma phenotypes during childhood. Regarding severe

asthma, high IgE levels to furry animals with complex allergen component patterns have been found (57). Several risk factors for uncontrolled pediatric asthma have been shown in a population-based Web survey, such as low birthweight, obesity, pet ownership before birth, and allergic comorbidities (especially AR) (58). Children with uncontrolled asthma present AR and obesity in half of the cases (59). It is debated whether systemic obesity-associated inflammation may modulate airway diseases. Actually, in a recent study, the obesity–asthma association was not explained by systemic inflammation (60).

The concept of endotypes, defined as disease subtypes on the basis of the underlying pathophysiology, recently emerged. A phenotype-/endotype-based classification approach could lead toward the application of stratified and personalized medicine (52). For asthma, three endotypes have been proposed with differences in clinical presentation and target of interventions. The most common in childhood is atopic asthma (Th2 high), responsive to inhaled corticosteroids and characterized by eosinophil airway inflammation and BHR (61). Intrinsic eosinophil non-atopic asthma (Th2 low) is distinguished by eosinophilia and BHR but no IgE response. Late-onset intrinsic non-eosinophil non-atopic asthma (Th2 low) seems to have a neutrophilic or a paucigranulocytic inflammation. Besides, moderate-to-severe asthma with poorer lung function has been associated with neutrophil inflammation (62).

Comorbidities of AR

AR is closely linked to comorbidities such as allergic conjunctivitis (30–71%) (63), asthma, otitis media with effusion and nasal polyps, besides atopic eczema (62). In addition, allergic nasal inflammation may lead to obstruction, decreased sinus ventilation, fluid accumulation, and bacterial infection, which can cause mucosal damage and frequently chronic sinusitis (64). Such AR comorbidities are used as markers of disease severity (44). Pollen-induced AR commonly correlates with oral symptoms after eating raw fruit, vegetables, and seeds (pollen-food syndrome), including labial and oropharyngeal pruritus and angioedema. This condition reflects the presence of IgE cross-reactivity between epitopes in pollen allergens, named 'panallergens', and homologous proteins in certain foods (65). A new pollen-food syndrome classification based on panallergen IgE sensitization profiles identified specific endotypes with the aim of developing tailored prevention and treatments in childhood (66). Moreover, atopic eczema and food allergy may precede the development of AR and asthma at school age (67, 68). Asthma onset is less commonly isolated than in subjects with AR and/or eczema in the second decade of life (13). Many children affected by AR have BHR, and several studies have supported AR as a risk factor for developing asthma (10). In the 'Environment and Childhood Asthma' birth cohort study, AR and asthma associated with atopic eczema or food allergy appeared closely linked with BHR and high FeNO levels among adolescents, especially among boys (69). The necessity of early diagnosis and treatment of both disorders to improve disease control and quality of life has been remarked. Furthermore, anaphylaxis,

which results from pollen antigen exposure in children with AR due to grass pollen allergen, has been rarely described (70).

Diagnostic assessment

Airway allergic diseases are commonly the result of exposure to pollens and perennial allergens, and rarely to airborne food allergens produced during cooking or food manipulation (71). Ordinarily, the diagnosis is based on clinical history confirmed by *in vivo* and/or *in vitro* specific IgE determinations, followed by allergen provocation tests when other investigations are inconclusive. In AR, clinical examination of the nose by anterior rhinoscopy demonstrates a pale/hyperemic swollen mucosa and is essential to rule out differential diagnoses such as nasal polyps (72). Inspecting spirometry tracings are necessary in the evaluation of children with asthma symptoms. Allergic sensitization is defined as skin prick tests (SPT) positivity or detection of serum sIgE. Measurement of IgE response to specific allergenic molecules through CRD is a second-line test useful to determine clinically relevant sensitizations to genuine allergens or cross-sensitization to panallergens (47). A great inconsistency (10–69%) between results of pollen SPT and CRD has been found in pollen-related AR diagnosis, mostly associated with panallergen sensitization (73). Recommendations for standardized methodologies and clinical use of FeNO measurement have been applied in adults and older children (74). However, FeNO values for atopic asthma diagnosis are not well defined and a large overlap in the distribution of FeNO levels from children with allergic asthma, non-allergic asthma, allergy without asthma, and healthy population has been reported (75). Besides, several potential confounders have been highlighted, such as age (74), gender, infection, race, atopic eczema (76), obesity, smoking, diet (alcohol, coffee), steroid intake, and menarche. Further investigations may be required in rhinitis, including nasal endoscopy for polyps, nasal mucociliary clearance measurement or nasal nitric oxide for primary ciliary dyskinesia, etc. (77). In cases having a history of wheezing characterized by spirometry anomalies but not responsive to therapy, alternative diagnoses must be considered. A careful examination of the flow–volume curves may indicate subglottic stenosis, tracheomalacia secondary to tracheo-esophageal fistula, double aortic arch, or vocal cord dysfunction (78).

Monitoring systems

Rhinitis control assessment often produces heterogeneous slopes in individual patients (79). Nevertheless, Demoly et al. (80) argued the concept of rhinitis control to improve clinical decisions. In the era of mobile technology, a new approach has been described as able to assist in diagnosis of seasonal AR in children and in the adherence assessment to treatment (81). Mobile-health generated a novel noninvasive tool for clinicians with great potential in the clinical diagnosis and monitoring of AR patients (82). Standardized questionnaires for evaluating the control of asthma and AR and patients' HRQoL have been used in recent years. Among these, Control of Allergic Rhinitis and Asthma Test for Children (CARATKids) has been

developed and validated in children aged 6–12 years (83). In addition, RHINASTHMA-Adolescents was based on the literature review, clinical experience, and unstructured interviews (84). Its development and validation have been revealed as useful for improving control of respiratory allergy in adolescents. Observing the degree of inflammation by local and systemic noninvasive biomarkers of Th2-mediated inflammation has been proposed to guide asthma management, such as exhaled breath condensate markers (H_2O_2 (85), pH levels (86)), blood and sputum eosinophils, FeNO (87), and serum periostin (88). These analyses are helpful, although they cannot be routinely performed. Notwithstanding that FeNO levels are dose-dependently reduced by oral steroid or inhaled corticosteroids (61, 89), tailoring treatment on FeNO values has not improved asthma control (90). In school-age children with persistent asthma, the highest morbidity was associated with both high FeNO and blood eosinophils but not with serum levels of periostin (91).

Therapeutic approaches

Medications

First-line treatment of AR is based on oral and/or intranasal antihistamines and intranasal corticosteroids (92). Recently, bilastine, a second-generation oral antihistamine, has shown to be tolerable in children from 2 years of age (93). Intranasal corticosteroids are considered the most adequate treatment for AR in children (94) and may be effective for coexisting conjunctivitis. Topical delivery has the advantage of minimizing systemic adverse effects with a fast onset. However, children often dislike the administration of topical nasal medications (95). Oral leukotriene receptor antagonist (montelukast) may be effective in AR, but only small pediatric studies have been performed to date (96). Moreover, in children with persistent AR, intranasal resveratrol plus carboxymethyl- β -glucan significantly reduced nasal symptoms (97) and some items concerning respiratory infections (such as school absences and days with fever) (98). In 'Th2-high' asthma endotype, the control strategy includes an increasing administration of drugs starting from low dose of ICS followed by medium/high doses of ICS alone or in combination with long-acting beta-2 agonist (LABA) or leukotriene receptor antagonist (LTRA). In patients with poorly controlled moderate-to-severe asthma, omalizumab, anti-IgE monoclonal antibody is recommended (99). Omalizumab has been found effective also for AR accompanied by an acceptable safety profile (100). Different therapeutic approaches have been proposed in uncontrolled 'Th2-high' asthma. Mepolizumab and reslizumab, which block the effects of IL-5, have been marketed recently in the United States for severe eosinophilic asthma in adults. Other not commercially available drugs include benralizumab, the antagonist of IL-5 receptor; dupilumab, monoclonal antibody binding to the IL4- α receptor for IL4 and IL13; lebrikizumab, IL-13 antagonist; ligelizumab, anti-IgE monoclonal antibody with a higher affinity for IgE than omalizumab (101, 102). Further choices in patients with mild-moderate asthma include vitamin D

supplementation, which a recent meta-analysis has found to reduce the frequency of asthma attacks and the need of oral steroid and hospitalization, irrespective of serum vitamin D levels (103). Inhaled vitamin A was useful in a randomized crossover study to alleviate the inflammatory process among asthmatic children (104), through immunomodulatory effects.

Healthcare provider–patient/parent collaboration is the key factor determining the success of guided self-management programs and adherence to daily therapy (73). Drama therapy has been used for education of adolescents having moderate–severe asthma and shows helpful results (72). Therapeutic goals of symptom relief, emotional/physical integration, and personal growth can be achieved by supportive methods.

Allergen-specific immunotherapy

Allergen-specific immunotherapy (AIT) with standardized allergen extracts is the only causal treatment potentially modifying the natural history of allergic airway diseases. The subcutaneous route (SCIT) has been widely studied; however, the procedure remains time-consuming and at risk of severe adverse reactions. During recent times, sublingual administration (SLIT) by drops or tablets has been found effective and safe (105). Nevertheless, immunotherapy in any form requires commitment by the patient, which makes adherence and compliance issues particularly relevant (106). The efficacy of AIT depends on correct patient selection, type of allergen, and product chosen for treatment. It has been found that CRD may be a fundamental diagnostic step to improve AIT efficacy among polysensitized children, since it permits prescribing AIT for allergens to which the patient is genuinely sensitized (73). AIT is accompanied by long-term efficacy, demonstrating a decreased immunologic reactivity after discontinuation (107, 108). AIT long-term benefit in children might be even better than in adults (109). Moreover, it has been underlined that AIT has a possible effect in reducing the prevalence of childhood respiratory infections (110).

Different regimens have been proposed in various trials: pre-seasonal, co-seasonal and continuous. At the first pollen season, SLIT continuous regimen for grass allergy performed better than the seasonal one, whereas in the second and third years two regimens were equivalent (111). Longitudinal studies and meta-analyses in adults (112) showed that a SLIT tablet containing five-grass pollens 300-IR is well tolerated and effective in reducing AR and conjunctivitis symptoms. Studies in pediatric populations have confirmed these benefits of pre- and co-seasonal treatments (113, 114). Significant effects were identified on symptom scores and medication scores in treated patients compared with the placebo group (115). Additionally, relevant effects were found even after one pre-/co-seasonal treatment period (116).

Treatment duration is based on individual clinical decisions and usually lasts for 3–5 years to induce prolonged symptom remission after cessation. Arroabarren et al. (117) found that 3 years of SCIT induced significant improvement in children with dust mite AR and asthma, while the five-year course added clinical improvement in AR.

AIT mechanisms of immune response have not been completely clarified. *In vitro* modifications have been associated with successful AIT: at third year, sIgG4 levels increased in all patients, persisting to be high at fifth year in five-year-treated patients, while decreasing in three-year-treated patients (117). A decrease in number of effector cells at inflammation focus (including mast cells, basophils, and eosinophils), together with a decrease in T-cell responsiveness to allergens, have been described in AIT-treated patients (118). AIT caused a significant decrease in transcription nuclear factor- κ B (NF- κ B) activation levels in neutrophils compared with neutrophils (119) and reduced the production of NF- κ B-dependent inflammatory mediators (IL-8 and TXA₂). This observation represents a novel view of neutrophils as a possible cell target to treat IgE-dependent diseases.

Novel ways of immunotherapy using compounds and peptides or recombinant allergens with or without mutations (120) are becoming realistic options in allergy practice (121). For example, subcutaneous use of depigmented polymerized extracts might allow rapid up-dosing and safe therapy with good tolerance and clinical response, as shown in a large pediatric retrospective analysis (122).

The most relevant limitation in AIT daily routine is the restricted use in patients affected by uncontrolled allergic asthma. Some clinical trials have shown that the combination of omalizumab and AIT clinically improves its effectiveness, with reduction in systemic adverse reaction risk (123). Moreover, some studies have evidenced that antihistamine pre-medication may decrease the rate of AIT adverse events (124, 125). Therefore, pre-treatment practice can develop AIT safety and efficacy and might be a useful approach to broaden the indication of AIT among allergic children.

Preventive approaches

Much effort is being placed on preventing allergic diseases (126). Primary prevention strategy focuses influence on the innate immune response and, as a consequence, the polarization of the adaptive immune responses (127). Immunologic intervention very early in infancy has been targeted to downgrade the overall propensity of the immune system to produce Th2-skewed responses to innocuous antigens. Thus, Holt et al. (128) recently proposed the sublingual administration of a mixture containing house-dust mite, cat, and timothy grass for high-risk children aged 12–30 months. However, after 3 years of treatment, SLIT did not prevent asthma or aerallergen sensitization.

Along with the concepts developed with the hygiene hypothesis, probiotics and bacterial lysates have been tested and their impact is still under investigation. So far, recommendations to families for primary prevention of respiratory allergies are still limited to avoid active and passive tobacco smoke (129).

In children with AR, AIT may have secondary preventive activity on the development of new allergic sensitizations (130) and on the development of asthma and BHR in children with AR sensitized to pollen or house-dust mites (131).

A prospective pilot study (132) investigated the sensitization-preventive effect of SLIT in mono/oligoclonally sensitized, clinically asymptomatic children aged 2–5 years. Preventive SLIT, over a period of 1–2 years, was safe; it did not enhance sensitization rate, while inducing a significant upregulation of allergen-specific IgG and IL-10-dependent inhibition. Additionally, it has been shown that IgE response against Phleum pratense very often evolves from a monosensitization stage to an oligomolecular sensitization stage to end up in a poly-molecular sensitization stage. This phenomenon has been defined as ‘molecular spreading’ (133). Finally, the evolution of the development of IgE sensitization was recently described about house-dust mite allergen molecules in the first two decades of life in the same cohort (134). The evidence of a molecular-spreading process calls for an earlier immunologic intervention with AIT targeted to prevent its clinical consequences (135).

Conclusions

As reported, there has been an explosion of numerous exciting advances on pediatric allergic airway diseases in recent years. These advances may lead to improve classification strategies with the purpose of a more accurate diagnosis and a patient-tailored therapy. This precision medicine represents the future of care in pediatric respiratory atopic diseases.

Acknowledgments

We thank Mr. Charles Clawson for revising the English language.

References

- Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. *J Allergy Clin Immunol* 2013; **131**: 23–30.
- Cibella F, Ferrante G, Cuttitta G, et al. The burden of rhinitis and rhinoconjunctivitis in adolescents. *Allergy Asthma Immunol Res* 2015; **7**: 44–50.
- Greiner AN, Hellings PW, Rotiroli G, Scadding GK. Allergic rhinitis. *Lancet* 2011; **378**: 2112–22.
- Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J* 2014; **7**: 12.
- Caminati M, Duric-Filipovic I, Arasi S, Peroni DG, Zivkovic Z, Senna G. Respiratory allergies in childhood: recent advances and future challenges. *Pediatr Allergy Immunol* 2015; **26**: 702–10.
- Hofmaier S. Allergic airway diseases in childhood: an update. *Pediatr Allergy Immunol* 2014; **25**: 810–6.
- Goronfolah L. Aeroallergens, atopy and allergic rhinitis in the Middle East. *Europ Annals Allergy Clin Immunol* 2016; **48**: 5–21.
- Radhakrishnan DK, Dell SD, Guttmann A, Shariff SZ, Liu K, To T. Trends in the age of diagnosis of childhood asthma. *J Allergy Clin Immunol* 2014; **134**: 1057–62 e5.
- Braun-Fahrlander C, Gassner M, Grize L, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Europ Res J* 2004; **23**: 407–13.
- Engelkes M, Janssens HM, de Ridder MA, de Jongste JC, Sturkenboom MC, Verhamme KM. Time trends in the incidence, prevalence and age at diagnosis of asthma in children. *Pediatr Allergy Immunol* 2015; **26**: 367–74.
- 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.
- Lockett GA, Huoman J, Holloway JW. Does allergy begin *in utero*? *Pediatr Allergy Immunol* 2015; **26**: 394–402.
- Gough H, Grabenhenrich L, Reich A, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatr Allergy Immunol* 2015; **26**: 431–7.
- Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev* 2011; **242**: 10–30.
- Li J, Zhang Y, Zhang L. Discovering susceptibility genes for allergic rhinitis and allergy using a genome-wide association study strategy. *Curr Opin Allergy Clin Immunol* 2015; **15**: 33–40.
- Chan WC, Sy HY, Kong AP, et al. Childhood asthma is associated with polymorphic markers of PROC on 2q14 in addition to 17q21 locus. *Pediatr Allergy Immunol* 2015; **26**: 173–80.
- Sarnowski C, Laprise C, Malerba G, et al. DNA methylation within melatonin receptor 1A (MTNR1A) mediates paternally transmitted genetic variant effect on asthma plus rhinitis. *J Allergy Clin Immunol* 2016; **138**: 748–53.
- Berankova K, Uhlik J, Honkova L, Pohunek P. Structural changes in the bronchial mucosa of young children at risk of developing asthma. *Pediatr Allergy Immunol* 2014; **25**: 136–42.
- Honkova L, Uhlik J, Berankova K, Svobodova T, Pohunek P. Epithelial basement membrane thickening is related to TGF- β 1 expression in children with chronic respiratory diseases. *Pediatr Allergy Immunol* 2014; **25**: 593–9.
- Liu AH. Revisiting the hygiene hypothesis for allergy and asthma. *J Allergy Clin Immunol* 2015; **136**: 860–5.
- Wu P, Feldman AS, Rosas-Salazar C, et al. Relative importance and additive effects of maternal and infant risk factors on childhood asthma. *PLoS One* 2016; **11**: e0151705.
- Murphy VE, Mattes J, Powell H, Baines KJ, Gibson PG. Respiratory viral infections in pregnant women with asthma are associated with wheezing in the first 12 months of life. *Pediatr Allergy Immunol* 2014; **25**: 151–8.
- Brandao HV, Vieira GO, de Oliveira Vieira T, et al. Increased risk of allergic rhinitis among children delivered by cesarean section: a cross-sectional study nested in a birth cohort. *BMC Pediatr* 2016; **16**: 57.
- Bager P, Melbye M, Rostgaard K, Benn CS, Westergaard T. Mode of delivery and risk of allergic rhinitis and asthma. *J Allergy Clin Immunol* 2003; **111**: 51–6.
- Thomas AO, Lemanske RF Jr, Jackson DJ. Infections and their role in childhood asthma inception. *Pediatr Allergy Immunol* 2014; **25**: 122–8.
- Hedlin G, Wahn U. More about asthma in PAI. *Pediatr Allergy Immunol* 2014; **25**: 110.
- Neuman A, Bergstrom A, Gustafsson P, et al. Infant wheeze, comorbidities and school age asthma. *Pediatr Allergy Immunol* 2014; **25**: 380–6.
- Hardjojo A, Goh A, Shek LP, et al. Rhinitis in the first 18 months of life: exploring the role of respiratory viruses. *Pediatr Allergy Immunol* 2015; **26**: 25–33.
- Camelo-Nunes I, Carvalho Mallozi M, Lanza FC, Sole D. Prevalence and

- associated factors for asthma in Brazilian and Japanese schoolchildren living in the city of Sao Paulo, Brazil. *Europ Annals Allergy Clin Immunol* 2016; **48**: 129–36.
30. Lombardi C, Fiocchi A, Raffetti E, et al. Cross-sectional comparison of the characteristics of respiratory allergy in immigrants and Italian children. *Pediatr Allergy Immunol* 2014; **25**: 473–80.
 31. Alvisi P, Brusa S, Alboresi S, et al. Recommendations on complementary feeding for healthy, full-term infants. *Ital J Pediatr* 2015; **41**: 36.
 32. Nwaru BI, Virtanen SM, Sheikh A. Key considerations for clinical trials of dietary interventions for primary prevention of allergy and asthma in children. *Pediatr Allergy Immunol* 2014; **25**: 730–2.
 33. Patel S, Custovic A, Smith JA, Simpson A, Kerry G, Murray CS. Cross-sectional association of dietary patterns with asthma and atopic sensitization in childhood – in a cohort study. *Pediatr Allergy Immunol* 2014; **25**: 565–71.
 34. Kerley CP, Hutchinson K, Cormican L, et al. Vitamin D3 for uncontrolled childhood asthma: a pilot study. *Pediatr Allergy Immunol* 2016; **27**: 404–12.
 35. Leung TF, Wang SS, Tang MF, et al. Childhood asthma and spirometric indices are associated with polymorphic markers of two vitamin D 25-hydroxylase genes. *Pediatr Allergy Immunol* 2015; **26**: 375–82.
 36. Kim YH, Kim KW, Kim MJ, et al. Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2016; **27**: 580–90.
 37. Larose TL, Chen Y, Camargo CA Jr, Langhammer A, Romundstad P, Mai XM. Factors associated with vitamin D deficiency in a Norwegian population: the HUNT Study. *J Epidemiol Community Health* 2014; **68**: 165–70.
 38. Arshi S, Ghalehbaghi B, Kamrava SK, Aminlou M. Vitamin D serum levels in allergic rhinitis: any difference from normal population? *Asia Pac Allergy* 2012; **2**: 45–8.
 39. Erkkola M, Kaila M, Nwaru BI, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 2009; **39**: 875–82.
 40. Wei Z, Zhang J, Yu X. Maternal vitamin D status and childhood asthma, wheeze, and eczema: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2016; **27**: 612–9.
 41. Chiu CY, Huang SY, Peng YC, et al. Maternal vitamin D levels are inversely related to allergic sensitization and atopic diseases in early childhood. *Pediatr Allergy Immunol* 2015; **26**: 337–43.
 42. Nissen SP, Kjaer HF, Host A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. *Pediatr Allergy Immunol* 2013; **24**: 549–55.
 43. Lukkariinen M, Vuorinen T, Lehtinen P, Ruuskanen O, Jartti T. Sensitization at the first wheezing episode increases risk for long-term asthma therapy. *Pediatr Allergy Immunol* 2015; **26**: 687–91.
 44. Dondi A, Tripodi S, Panetta V, et al. Pollen-induced allergic rhinitis in 1360 Italian children: comorbidities and determinants of severity. *Pediatr Allergy Immunol* 2013; **24**: 742–51.
 45. Gabet S, Just J, Couderc R, Bousquet J, Seta N, Momas I. Early polysensitization is associated with allergic multimorbidity in PARIS birth cohort infants. *Pediatr Allergy Immunol* 2016; in press.
 46. de Jong AB, Dikkeschei LD, Brand PL. Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, monosensitized, and polysensitized children. *Pediatr Allergy Immunol* 2011; **22**: 166–71.
 47. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI molecular allergology user's guide. *Pediatr Allergy Immunol* 2016; **27**(Suppl 23): 1–250.
 48. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; **108**(5 Suppl.): S147–334.
 49. Jauregui I, Davila I, Sastre J, et al. Validation of ARIA (Allergic Rhinitis and its Impact on Asthma) classification in a pediatric population: the PEDRIAL study. *Pediatr Allergy Immunol* 2011; **22**: 388–92.
 50. Valero A, Ferrer M, Sastre J, et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the Allergic Rhinitis and its Impact on Asthma severity items. *J Allergy Clin Immunol* 2007; **120**: 359–65.
 51. Montoro J, Del Cuvillo A, Mullol J, et al. Validation of the modified allergic rhinitis and its impact on asthma (ARIA) severity classification in allergic rhinitis children: the PEDRIAL study. *Allergy* 2012; **67**: 1437–42.
 52. Papadopoulos NG, Bernstein JA, Demoly P, et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. *Allergy* 2015; **70**: 474–94.
 53. Kurukulaaratchy RJ, Zhang H, Patil V, et al. Identifying the heterogeneity of young adult rhinitis through cluster analysis in the Isle of Wight birth cohort. *J Allergy Clin Immunol* 2015; **135**: 143–50.
 54. Arasi S, Pajno GB, Lau S, Matricardi PM. Local allergic rhinitis: a critical reappraisal from a paediatric perspective. *Pediatr Allergy Immunol* 2016; **27**: 569–73.
 55. Zicari AM, Occasi F, Di Fraia M, et al. Local allergic rhinitis in children: novel diagnostic features and potential biomarkers. *Am J Rhinol Allergy* 2016; **30**: 329–34.
 56. Just J, Saint Pierre P, Amat F, et al. What lessons can be learned about asthma phenotypes in children from cohort studies? *Pediatr Allergy Immunol* 2015; **26**: 300–5.
 57. Konradsen JR, Nordlund B, Onell A, Borres MP, Gronlund H, Hedlin G. Severe childhood asthma and allergy to furry animals: refined assessment using molecular-based allergy diagnostics. *Pediatr Allergy Immunol* 2014; **25**: 187–92.
 58. Sasaki M, Yoshida K, Adachi Y, et al. Factors associated with asthma control in children: findings from a national Web-based survey. *Pediatr Allergy Immunol* 2014; **25**: 804–9.
 59. Ferreira-Magalhaes M, Pereira AM, Sa-Sousa A, et al. Asthma control in children is associated with nasal symptoms, obesity, and health insurance: a nationwide survey. *Pediatr Allergy Immunol* 2015; **26**: 466–73.
 60. Lu Y, Van Bever HP, Lim TK, et al. Obesity, asthma prevalence and IL-4: roles of inflammatory cytokines, adiponectin and neuropeptide Y. *Pediatr Allergy Immunol* 2015; **26**: 530–6.
 61. Kinaciyan T, Jahn-Schmid B, Radakovics A, et al. Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. *J Allergy Clin Immunol* 2007; **119**: 937–43.
 62. Bertelsen RJ, Carlsen KC, Carlsen KH. Rhinitis in children: co-morbidities and phenotypes. *Pediatr Allergy Immunol* 2010; **21**: 612–22.
 63. Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol* 2015; **15**: 482–8.
 64. Rotiroti G, Roberts G, Scadding GK. Rhinitis in children: common clinical presentations and differential diagnoses. *Pediatr Allergy Immunol* 2015; **26**: 103–10.
 65. McKenna OE, Asam C, Araujo GR, Roulias A, Goulart LR, Ferreira F. How relevant is panallergen sensitization in the development of allergies? *Pediatr Allergy Immunol* 2016; **27**: 560–8.

66. Mastrorilli C, Tripodi S, Caffarelli C, et al. Endotypes of pollen-food syndrome in children with seasonal allergic rhinoconjunctivitis: a molecular classification. *Allergy* 2016; **71**: 1181–91.
67. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. *Pediatr Allergy Immunol* 2013; **24**: 476–86.
68. Cipriani F, Dondi A, Ricci G. Recent advances in epidemiology and prevention of atopic eczema. *Pediatr Allergy Immunol* 2014; **25**: 630–8.
69. Hovland V, Riiser A, Mowinkel P, Carlsen KH, Carlsen KC. Asthma with allergic comorbidities in adolescence is associated with bronchial responsiveness and airways inflammation. *Pediatr Allergy Immunol* 2014; **25**: 351–9.
70. Haluk Akar H, Akif Goktas M, Tahan F. Grass pollen triggered anaphylaxis in an adolescent boy. *Europ Annals Allergy Clin Immunol* 2015; **47**: 20–1.
71. Leonardi S, Pecoraro R, Filippelli M, et al. Allergic reactions to foods by inhalation in children. *Allergy Asthma Proceed* 2014; **354**: 288–94.
72. Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in rhinology EAACI position paper. *Clin Transl Allergy* 2011; **11**: 2.
73. Stringari G, Tripodi S, Caffarelli C, et al. The effect of component-resolved diagnosis on specific immunotherapy prescription in children with hay fever. *J Allergy Clin Immunol* 2014; **134**: 75–81.
74. Heijkenskjold-Rentzhog C, Kalm-Stephens P, Nordvall L, Malinovski A, Alving K. New method for single-breath fraction of exhaled nitric oxide measurement with improved feasibility in preschool children with asthma. *Pediatr Allergy Immunol* 2015; **26**: 662–7.
75. Tang S, Xie Y, Yuan C, Sun X, Cui Y. Fractional exhaled nitric oxide for the diagnosis of childhood asthma: a systematic review and meta-analysis. *Clin Rev Allergy Immunol* 2016; in press.
76. Zinelli C, Caffarelli C, Strid J, Jaffe A, Atherton DJ. Measurement of nitric oxide and 8-isoprostane in exhaled breath of children with atopic eczema. *Clin Exp Dermatol* 2009; **34**: 607–12.
77. Gane SB, Scadding GK. Diseases mimicking allergic rhinitis. *Pediatr Allergy Immunol* 2010; **21** Pt 2: e114–8.
78. de Benedictis FM, de Benedictis D, Mirabile L, Pozzi M, Guerrieri A, Di Pillo S. Ground zero: not asthma at all. *Pediatr Allergy Immunol* 2015; **26**: 490–6.
79. Florack J, Brighetti MA, Perna S, et al. Comparison of six disease severity scores for allergic rhinitis against pollen counts a prospective analysis at population and individual level. *Pediatr Allergy Immunol* 2016; **27**: 382–90.
80. Demoly P, Calderon MA, Casale T, et al. Assessment of disease control in allergic rhinitis. *Clin Transl Allergy* 2013; **3**: 7.
81. Tripodi S, Comberiati P, Di Rienzo Businco A. A web-based tool for improving adherence to sublingual immunotherapy. *Pediatr Allergy Immunol* 2014; **25**: 611–2.
82. Costa C, Menesatti P, Brighetti MA, et al. Pilot study on the short-term prediction of symptoms in children with hay fever monitored with e-Health technology. *Europ Annals Allergy Clin Immunol* 2014; **46**: 216–25.
83. Linhares DV, da Fonseca JA, Borrego LM, et al. Validation of control of allergic rhinitis and asthma test for children (CARATKids) – a prospective multicenter study. *Pediatr Allergy Immunol* 2014; **25**: 173–9.
84. La Grutta S, Landi M, Braido F, et al. RHINASTHMA-Adolescents: a new quality of life tool for patients with respiratory allergy. *Pediatr Allergy Immunol* 2014; **25**: 450–5.
85. Caffarelli C, Calcinai E, Rinaldi L, Povesi Dascola C, Terracciano L, Corradi M. Hydrogen peroxide in exhaled breath condensate in asthmatic children during acute exacerbation and after treatment. *Respiration* 2012; **84**: 291–8.
86. Caffarelli C, Dascola CP, Peroni D, et al. Airway acidification in childhood asthma exacerbations. *Allergy Asthma Proceed* 2014; **353**: 51–6.
87. Di Cara G, Marcucci F, Palomba A, et al. Exhaled nitric oxide in children with allergic rhinitis: a potential biomarker of asthma development. *Pediatr Allergy Immunol* 2015; **26**: 85–7.
88. Inoue T, Akashi K, Watanabe M, et al. Periostin as a biomarker for the diagnosis of pediatric asthma. *Pediatr Allergy Immunol* 2016; **27**: 521–6.
89. Manna A, Caffarelli C, Varini M, et al. Clinical application of exhaled nitric oxide measurement in pediatric lung diseases. *Ital J Pediatr* 2012; **38**: 74.
90. Petsky HL, Cates CJ, Lasserson TJ, et al. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* 2012; **67**: 199–208.
91. Konradsen JR, Skantz E, Nordlund B, et al. Predicting asthma morbidity in children using proposed markers of Th2-type inflammation. *Pediatr Allergy Immunol* 2015; **26**: 772–9.
92. Wert AF, Posa D, Tsilochristou O, Schwerk N. Treatment of allergic children – where is the progress? (for the practicing allergist). *Pediatr Allergy Immunol* 2016; **27**: 671–681.
93. Novak Z, Yanez A, Kiss I, et al. Safety and tolerability of bilastine 10 mg administered for 12 weeks in children with allergic diseases. *Pediatr Allergy Immunol* 2016; **27**: 493–8.
94. Kaszuba SM, Baroody FM, deTineo M, Haney L, Blair C, Naclerio RM. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. *Arch Intern Med* 2001; **161**: 2581–7.
95. Wong IY, Soh SE, Chng SY, et al. Compliance with topical nasal medication – an evaluation in children with rhinitis. *Pediatr Allergy Immunol* 2010; **21**: 1146–50.
96. Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 2013; **68**: 1102–16.
97. Varricchio AM, Capasso M, Della Volpe A, et al. Resveratrol plus carboxymethyl-beta-glucan in children with recurrent respiratory infections: a preliminary and real-life experience. *Ital J Pediatr* 2014; **40**: 93.
98. Miraglia Del Giudice M, Maiello N, Decimo F, et al. Resveratrol plus carboxymethyl-beta-glucan may affect respiratory infections in children with allergic rhinitis. *Pediatr Allergy Immunol* 2014; **25**: 724–8.
99. Rodrigo GJ, Neffen H. Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents. *Pediatr Allergy Immunol* 2015; **26**: 551–6.
100. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004; **59**: 709–17.
101. Riedler J. Pediatric Asthma – do we need more innovation for treatment? *Pediatr Allergy Immunol* 2014; **25**: 19–20.
102. Stokes JR, Casale TB. Characterization of asthma endotypes: implications for therapy. *Annals Allergy Asthma Immunol* 2016; **117**: 121–5.
103. Martineau AR, Cates CJ, Urashima M, et al. Vitamin D for the management of asthma. *Cochrane Database Syst Rev*. 2016; **9**: CD011511.
104. Reifen R, Berkovich Z, Mandelberg A. Vitamin A supplementation via aerosol

- spray in asthmatic children. *Pediatr Allergy Immunol* 2015; **266**: 578–9.
105. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011; **666**: 740–52.
 106. Vita D, Caminiti L, Ruggeri P, Pajno GB. Sublingual immunotherapy: adherence based on timing and monitoring control visits. *Allergy* 2010; **655**: 668–9.
 107. Durham SR, Emminger W, Kapp A, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010; **1251**: 131–8 e1–7.
 108. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999; **3417**: 468–75.
 109. Calderon MA, Gerth van Wijk R, Eichler I, et al. Perspectives on allergen-specific immunotherapy in childhood: an EAACI position statement. *Pediatr Allergy Immunol* 2012; **234**: 300–6.
 110. Occasi F, De Castro G, Zicari AM, Indinnimeo L, Tancredi G, Duse M. Sublingual immunotherapy in children and its potential beneficial collateral effect on respiratory tract infections. *Curr Med Res Opin* 2015; **315**: 939–41.
 111. Pajno GB, Caminiti L, Crisafulli G, et al. Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: a randomized controlled study. *Pediatr Allergy Immunol* 2011; **228**: 803–7.
 112. Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007; **1206**: 1338–45.
 113. Eberle P, Brueck H, Gall R, Hadler M, Sieber J, Karagiannis E. An observational, real-life safety study of a 5-grass pollen sublingual tablet in children and adolescents. *Pediatr Allergy Immunol* 2014; **258**: 760–6.
 114. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; **1231**: 167–73 e7.
 115. Wahn U, Klimek L, Ploszczuk A, et al. High-dose sublingual immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2012; **1304**: 886–93 e5.
 116. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014; **71**: 6.
 117. Arroabarren E, Tabar AI, Echechipia S, Cambra K, Garcia BE, Alvarez-Puebla MJ. Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy. *Pediatr Allergy Immunol* 2015; **261**: 34–41.
 118. Durham SR, Varney VA, Gaga M, et al. Grass pollen immunotherapy decreases the number of mast cells in the skin. *Clin Exp Allergy* 1999; **2911**: 1490–6.
 119. Ventura I, Vega A, Chamorro C, et al. Allergen immunotherapy decreases LPS-induced NF-kappaB activation in neutrophils from allergic patients. *Pediatr Allergy Immunol* 2014; **252**: 129–35.
 120. Rose K, Kopp MV. Pediatric investigation plans for specific immunotherapy: questionable contributions to childhood health. *Pediatr Allergy Immunol* 2015; **268**: 695–701.
 121. Wahn U. Will novel products for immunotherapy be available for children in the future? *Pediatr Allergy Immunol* 2015; **268**: 694.
 122. Pfaar O, Sager A, Robinson DS. Safety and effect on reported symptoms of depigmented polymerized allergen immunotherapy: a retrospective study of 2927 paediatric patients. *Pediatr Allergy Immunol* 2015; **263**: 280–6.
 123. Kopp MV. Role of immunomodulators in allergen-specific immunotherapy. *Allergy* 2011; **666**: 792–7.
 124. Morris AE, Marshall GD Jr. Safety of allergen immunotherapy: a review of premedication and dose adjustment. *Immunotherapy* 2012; **43**: 315–22.
 125. Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Annals Allergy* 1994; **735**: 409–18.
 126. Nieto A, Wahn U, Bufe A, et al. Allergy and asthma prevention 2014. *Pediatr Allergy Immunol* 2014; **256**: 516–33.
 127. Holt PG. Prevention—what is the most promising approach? *Pediatr Allergy Immunol* 2014; **251**: 12–4.
 128. Holt PG, Sly PD, Sampson HA, et al. Prophylactic use of sublingual allergen immunotherapy in high-risk children: a pilot study. *J Allergy Clin Immunol* 2013; **1324**: 991–3 e1.
 129. Hamelmann E, Beyer K, Gruber C, et al. Primary prevention of allergy: avoiding risk or providing protection? *Clin Exp Allergy* 2008; **382**: 233–45.
 130. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997; **994**: 450–3.
 131. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; **1092**: 251–6.
 132. Szepfalusi Z, Bannert C, Ronceray L, et al. Preventive sublingual immunotherapy in preschool children: first evidence for safety and pro-tolerogenic effects. *Pediatr Allergy Immunol* 2014; **258**: 788–95.
 133. Hatzler L, Panetta V, Lau S, et al. Molecular spreading and predictive value of preclinical IgE response to Phleum pratense in children with hay fever. *J Allergy Clin Immunol* 2012; **1304**: 894–901 e5.
 134. Posa D, Perna S, Resch Y, et al. Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. *J Allergy Clin Immunol* 2016; in press.
 135. Matricardi PM. Allergen-specific immunoprophylaxis: toward secondary prevention of allergic rhinitis? *Pediatr Allergy Immunol* 2014; **251**: 15–8.