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Treatment of allergic children - where is the progress? (for the practicing allergist)

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List of abbreviations used:

AD: Atopic dermatitis

AIT: Allergen-specific Immunotherapy

AR: Allergic rhinitis

CSU: Chronic spontaneous urticaria

C1 INH: C1 esterase inhibitor

EAI: Epinephrine autoinjector

EMA: European Medicine Agency

FDA: Food and Drug Administration

HAE: hereditary angioedema

ICS: Inhaled corticosteroids

INS: Intranasal corticosteroids

LABA: Long-acting beta-2 adrenergic agonists

OIT: Oral immunotherapy

PIP: Pediatric investigational Plan

SCIT: Subcutaneous allergen immunotherapy

SLIT: Sublingual immunotherapy

SNP: Single nucleotide polymorphism

TCI: Topical calcineurin inhibitors

VDR: Vitamin D receptor

VKC: Vernal keratoconjunctivitis

HMGB-1: high-mobility group box-1

sRAGE: serum soluble receptor for advanced glycation end products

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For any kind of therapeutic intervention in allergic diseases such as environmental control, pharmacological or immunomodulating treatment including educational programs, children are addressed separately from adults. Health authorities like the Food and Drug Administration (FDA) in the United States of America or the European Medicine Agency (EMA) in Europe request a specific „Pediatric investigational Plan“ (PIP) with studies addressing dose-response relationship, safety and efficacy for infants, children, and adolescents. During the last two years promising advances have been

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reported for the treatment of a variety of allergic and immunologic disorders. This review summarizes the progress in the treatment of pediatric asthma and allergic diseases, based on publications of approximately the last 2.5 years (end of 2013 until May 2016) in and beyond this journal. Meanwhile, it highlights areas with promising novel therapeutic approaches, which are likely to change treatment for allergic children in the near future.

Atopic dermatitis:

Atopic dermatitis (AD), a chronic pathologic skin condition, is one of the 50 most prevalent diseases in childhood and often the first manifestation of atopy in infancy.¹ Its pathogenesis is related to increased water loss due to a defective skin epidermal barrier. Emollients are known to provide a safe and effective method of skin barrier enhancement.² Therefore they have been recommended as everyday and first line therapy during acute flares as well as remission.^{3,4} A non-steroidal, anti-inflammatory moisturizing cream containing a polysaccharide obtained by bacterial fermentation (rhanmosoft®), ceramides and L-isoleucine (pro-AMP cream)⁵ has been recently developed for the specific treatment of AD. In a randomized, controlled trial Marsegia et al. showed pro-AMP cream to be more effective in comparison with an emollient creme in the treatment of mild-to-moderate chronic AD-lesions of the face.⁵

Topical corticosteroids are commonly used as first-line treatment of AD exacerbations.⁶ Concerns about side effects and the side effects themselves have in many cases led to increased second-line use of topical calcineurin inhibitors (TCI). For patients 2-years and older two preparations, pimecrolimus 1% cream and tacrolimus 0,03% ointment, are available. In 2006, FDA issued a boxed warning requirement based on the theoretical risk of skin malignancies and lymphoma. Nonetheless, recent studies found no significant association between malignancies and topical use of pimecrolimus and tacrolimus.⁷⁻¹¹ This compelling body of evidence does not seem to support the safety concerns FDA added in the boxed warnings for TCIs. Therefore, an increasing number of experts in the field recommend the reconsideration of the validity of the boxed warning for TCIs and conclude that pimecrolimus cream and, based on more limited published reports, tacrolimus ointment, are safe and effective for the treatment of infants at least 3 months of age with AD.¹⁰

During the last years a variety of preventative approaches aiming at a reduction of the incidence as well as the treatment of atopic dermatitis have been studied:

1) In 2014 two pilot studies have reported that application of moisturizers to neonates prevents the development of atopic dermatitis.^{12,13} Simpson et al.¹³ reported a 50% relative risk reduction at 6 months of age when parents applied full-body emollient therapy, once a day, in high risk neonates within 3 weeks from birth. Although these findings are promising, the study presents methodological difficulties¹⁴ and therefore, larger, more rigorous future studies are needed.

2) Probiotics have been suggested as an intervention to prevent allergic diseases. It has recently been shown that probiotic supplementation can have an effect in modifying genetic susceptibility to eczema in high-risk children.¹⁵ In addition, new data show that probiotic supplementation can modulate specific toll-like receptor genotypes.¹⁶ Moreover, a recent meta-analysis of randomized trials by Cuello-Garcia et al.¹⁷ found a

reduced risk of eczema in infants if probiotics were used by pregnant women, breastfeeding mothers or given to infants. The authors however stated a low certainty in the evidence the retrieved literature reports.¹⁷

3) Epidemiological data on infant feeding practices and allergic diseases are controversial. Current feeding guidelines recommend exclusive breastfeeding for 4-6 months.¹⁸ Recent studies suggested that delayed introduction of solid foods may even increase the risk of AD.^{19,20} Data from Turati et al.²¹ show that early weaning, defined as the introduction of solid foods at 4 or 5 months of age, is inversely related to the risk of AD development; children weaned at 4 or 5 months had lower AD risk compared to those exclusively breastfed. In addition, introduction of a high number of different solid foods reduced the risk of AD.²¹

4) Existing literature on the influence of vitamin D in the development of allergic diseases is contradictory.^{22,23} Recently Wang et al. have shown that vitamin D deficiency is associated with childhood AD and high total IgE in Hong Kong Chinese children.²⁴ Further to these results, vitamin D supplementation might be an effective treatment in reducing AD severity in children as suggested by Di Filippo et al.²⁵ who treated 39 AD-children with vitamin D 1000 IU/day for 3 months. They recorded reduction in the SCORAD index and demonstrated immunological effects by showing a change of the Th1 and Th2 interleukin serum pattern.²⁵ The same promising results arise from a randomized placebo controlled study in which Camargo et al. demonstrated that vitamin D (1000 IU/day) supplementation improved winter-related AD in Mongolian children.²⁶ Additional trials are needed in other populations and settings before regular vitamin D supplementation can be recommended for the treatment of children with AD. Furthermore cut-off levels of serum vitamin D levels have to be defined for treatment decisions.

Besides therapeutics and preventive measures, much attention is gathered around family educational programs for AD. Ahrens et al.²⁷ reviewed existing educational strategies and concluded that there is enough evidence to integrate appropriate programs routinely into the treatment of AD-children that will ultimately empower the affected child and its caregivers to obtain best possible care, prevention, and quality of life. Nevertheless, a Cochrane systematic review²⁸ highlights the relative lack of rigorously designed trials to support the effectiveness of educational and psychological interventions in helping to manage AD in children. However, the authors also mention that some pediatric studies using different educational intervention delivery models (multiprofessional eczema interventions and nurse-led clinics²⁹) have resulted in improvements in disease severity and quality of life.^{27,28}

Asthma:

The Global Initiative for Asthma (GINA) management and prevention has published recommendations for the diagnosis, assessment and treatment of asthma. Inhaled corticosteroids (ICS) represent the cornerstone of treatment for persistent asthma in school-aged children.^{30,31} Data in ≤ 5 years old children in Norway showed a high prevalence of ICS prescription but a low persistence within several preschool years, suggesting that ICS are frequently given for intermittent asthma-like symptoms in preschoolers.³² Asthma guidelines suggest a restrictive use of ICS during the first years of life and on this basis, a recent systematic review³³ took into account randomised

controlled trials comparing daily use of ICS, delivered by any type of inhalation device for at least three months, versus placebo or non-steroidal drugs in children up to 18 years of age with persistent asthma. The authors concluded that daily use of low or medium ICS doses can cause a small (approximately half a centimeter per year less than those not treated with these medications during the first year of treatment) reduction in height in children up to 18 years of age with persistent asthma. Furthermore it has to be questioned whether the reduced height is related to the steroids or to the disease per se and/or the course of the disease. Further studies in this field are needed. In the same context, Sidoroff et al.³⁴, having followed up a cohort of early childhood wheezers, report that ICS use during childhood may be related to a decrease in bone marrow density in late school age. Nonetheless, such effects seems minor as opposed to the known benefits of these medications in asthma control.

Long-acting beta-2 adrenergic agonists (LABA), including salmeterol and formoterol, have long lasting bronchodilator action. All position papers agree that LABA should only be prescribed in combination with ICS, and are therefore relevant as add-on treatment.³⁰ A cochrane review focused on randomised controlled trials comparing single-inhaler therapy with budesonide/formoterol (SiT) (maintenance as well reliever) versus combination inhalers at a higher maintenance dose of steroids (either salmeterol/fluticasone or budesonide/formoterol) than was given in the SiT arm, plus additional fast-acting beta2-agonists as relievers. Studies involved adults and only children ≥ 12 years of age and the authors of the review concluded that SiT reduced the number of patients having asthma exacerbations requiring oral steroids and the number requiring hospitalisation or an ER visit compared with fixed-dose combination inhalers.³⁵ In addition, the mean daily dose of ICS in SiT, including the total dose administered with reliever use, was always lower than that of the other combination groups. No studies have yet addressed the efficacy of SiT budesonide/formoterol as maintenance and reliever therapy in children younger than age 12.

Recently a group from Finland studied the effect of systemic prednisolone treatment in the first acute, rhinovirus-induced wheezing episode in young children and found it to be without effect on long-term, ie within 12-months from the episode, outcome.³⁶

Leukotriene receptor antagonists are regarded as second line controller medication in pediatric asthma management. Stelmach et al.³⁷ aimed to determine in a randomized, double-blinded trial the effects of montelukast added to maintenance ICS therapy during the school year in children with stable asthma. They demonstrated that montelukast lowered the cumulative ICS dose, as well as reduced the number of exacerbations, and achieved better control of exercised-induced bronchoconstriction. Meanwhile, a systematic review of existing literature concluded that montelukast may also reduce the frequency of post-bronchiolitic wheezing, without causing significant side effects, but it has no impact in decreasing incidences of recurrent wheezing, symptom-free days, or the usage of corticosteroids.³⁸

Omalizumab, the anti-IgE monoclonal antibody, is an immunomodulating therapeutic approach in childhood asthma, now indicated for children 6 years and older with moderate to severe persistent asthma, having a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS.³⁹ Deschildre et al. followed up allergic, severe asthmatic children (6–18 years) who

received omalizumab for two years and reported a significant reduction in severe exacerbation rate. Nonetheless, the cessation rate of omalizumab during the second year was high (20.7%).⁴⁰ A systematic review of randomized controlled trials also supports the efficacy of add-on omalizumab in patients with moderate-to-severe allergic asthma in addition to an acceptable safety profile.⁴¹ Although omalizumab is generally administered for long-term periods, Teach et al.⁴² explored the effect of adding it for short-term versus ICS versus placebo to inner-city asthmatic children before they return to school at fall. The fall exacerbation rate was significantly lower in the omalizumab versus placebo arms, but there was no significant difference between omalizumab and ICS boost. Especially in the participants with an exacerbation during the run-in phase, omalizumab was significantly more efficacious than both placebo and ICS boost.⁴² Last but not least, a state-of-the-art review on the management of severe asthma in childhood reminds us that this group of asthmatic children require a standardized and individualized approach including reassessment for differential diagnosis, comorbidities, aggravating factors and allergy among others.⁴³

Subcutaneous allergen immunotherapy (SCIT) on the other hand, is a causal treatment option. It is, however, contraindicated for patients with severe unstable persistent asthma. Nonetheless, observations in a limited number of children and adolescents with severe persistent asthma suggest that pre-treatment with omalizumab before SCIT seems to improve the safety and probably also the efficacy of SCIT.^{44,45} This will require further confirmation.

In a recent study with adult patients it was shown that the addition of tiotropium to the regime was superior to doubling the dose of ICS and equivalent to adding a LABA.⁴⁶ Meanwhile, children and adolescents with moderate asthma presented significant improvement in lung function when tiotropium was added to ICS maintenance therapy and it was safe and well tolerated.⁴⁷⁻⁴⁹

Efficacy results on macrolides for the treatment of asthma are controversial. A cochrane review of randomised controlled clinical trials found no evidence for macrolides to be better than placebo for the majority of clinical outcomes.⁵⁰ Following the publication of this review, Stokholm et al. showed in a randomised, double-blind, placebo-controlled trial, that azithromycin reduced the duration of episodes of asthma-like symptoms in young (1-3 years old) wheezy children.⁵¹ Whether this was an immunomodulating effect or an antimicrobial effect in some children with undetected protracted bacterial bronchitis with wheeze is not clear. For further studies a better description of asthma endotypes and a discrimination between asthmatic children and children with protracted bacterial bronchitis-induced wheeze is therefore absolutely mandatory.

As mentioned above the data on the impact of vitamin D supplementation for the primary prevention and/or management of atopic diseases and asthma have been quite dubious so far. Recently, a group from Tokyo demonstrated that low-dose, short term vitamin D supplementation in addition to standard treatment may improve levels of asthma control in school children.⁵² Moreover, Einisman et al. report a possible association of vitamin D status and a single nucleotide polymorphism (SNP) (FokI C allele) in the gene encoding the vitamin D receptor (VDR) with higher requirement of therapy to reach asthma control in children.⁵³ Further to this study, a systematic search and meta-analysis of the literature reveals that besides FokI, other two SNPs (TaqI, and

BsmI) VDR contribute to asthma susceptibility.⁵⁴ Further trials are awaited to provide definite clues about the role of vitamin D in asthma.

Besides the therapeutic regime chosen, adherence to asthma therapy is a key determinant of asthma control. There is evidence that comprehensive, guideline-based asthma self-management programmes can be successful. Patient-centered care and shared decisions seem to be key factors determining the success of these programmes.⁵⁵ In asthmatic adolescents educational drama can be helpful in asthma management but more studies investigating various asthma parameters will help better understand the role of drama in asthma education and management.⁵⁶

Allergic Rhinitis:

Rhinitis is a common and often unrecognized problem in childhood and adolescence and impacts negatively on physical, social and psychological well-being. The diagnosis of allergic rhinitis (AR) is mainly based on the clinical history confirmed by in vivo and/or in vitro specific IgE determinations as well as allergen provocation tests when patients' history and/or in vivo and/or in vitro tests are inconclusive. A novel case report sets new horizons as it indicates that mobile-health can assist in the diagnosis of seasonal AR in polysensitized children, using the smartphone as a new diagnostic tool.⁵⁷ Meanwhile, the use of smartphones and electronic clinical diaries has also introduced new possibilities for the monitoring of adherence to treatment of children with allergic rhinitis.⁵⁸ These findings suggest that mobile-health, a novel noninvasive tool for clinicians, warrants further investigation in order to confirm its usefulness and potential in the clinical diagnosis and monitoring of AR patients.

Oral and/or intranasal antihistamines and nasal corticosteroids are both appropriate for first-line AR treatment although the latter are more effective.⁵⁹ Bilastine is a second-generation oral H1-antihistamine approved for the treatment of allergic rhinoconjunctivitis in adults and adolescents from 12 years of age. It is usually administered in a once-daily dose of 20mg. Recently it has been shown that a 10-mg dose of bilastine in children aged 2 to 11 years provides an equivalent systemic exposure as a 20mg dose in adults.⁶⁰ Additionally, a phase III, double-blind study showed bilastine 10mg to be safe and tolerable in children with allergic rhinoconjunctivitis.⁶¹

Corticosteroids address the inflammatory component of AR, and results from a large number of well-designed studies recommend their use in children and adolescents from 2 years old.⁶² MP-AzeFlu is a novel formulation that combines azelastine hydrochloride, and fluticasone propionate in a single spray. Its efficacy and safety in adults and adolescents with AR is well documented.^{63,64} In children the treatment effect of intranasal steroids has been shown to be lower^{65,66} and a possible confounder in these studies has been assumed to be the assessment of symptoms by the caregiver, since there can be a discrepancy between the symptoms reported by them versus children.⁶⁷⁻⁶⁹ A study published in the beginning of 2016, besides reporting that MP-AzeFlu is an effective treatment for childhood-AR, highlights that caregivers are less able than children to accurately assess response to treatment with available tools.⁶⁹ Recent data from Berger and colleagues have shown that MP-AzeFlu provides significantly greater, more rapid and clinically-relevant symptom relief than fluticasone propionate alone in

children aged 6 to 12 with AR.⁶⁷ In this study confounders have been minimized using a simple scoring system for the assessment of efficacy.

The only treatment potentially able to modify the natural history of AR and to prevent the onset of new sensitizations is allergen—specific immunotherapy (AIT).⁷⁰⁻⁷⁵ The term 'specific immunoprophylaxis' refers to the early administration of a specific kind of immunotherapy to healthy children with serum-specific-IgE and a positive family history aiming to prevent or delay AR onset.^{70,76}

Sensitization to profilins and other cross-reacting molecules might hinder proper AIT prescription in polysensitized patients. Stringari and colleagues suggested to consider component resolved analysis as a diagnostic step after skin prick test to improve AIT efficacy.⁷⁷ Although making a targeted choice in AIT prescription is fundamental, the optimal duration of AIT remains a debated issue. On this basis, a prospective study aimed to address the clinical efficacy of three versus five years of SCIT in children with dust mite respiratory allergy. The authors presented data according to which three years of SCIT induced significant improvement but that a 5-year course added clinical improvement in rhinitis.⁷⁸

The use of SCIT can be limited to some extent due to potential side effects including anaphylaxis. A large retrospective survey analysing real-life data of almost 3000 children and adolescents suggests that SCIT with depigmented polymerized pollen or mite extracts reduces symptoms and is well tolerated.⁷⁹

On the other hand, sublingual immunotherapy (SLIT) is also effective in AR and has an optimal safety and tolerability profile.^{70,71} Only rare cases of anaphylaxis have been reported so far.^{80,81} It has been shown that in patients receiving SCIT asthma is a risk factor for systemic reactions⁸² which does not seem to be the case for SLIT. Indeed, a post-hoc analysis of data from randomized, double-blind, placebo-controlled trials of SLIT Timothy grass tablet reports it did not increase the frequency of adverse events or systemic allergic reactions in adults and children with well-controlled mild asthma versus the non-asthmatic subjects.⁸³

Recently, a study from Eberle et al. demonstrated that in routine clinical practice, pre- and co-seasonal treatment with a 300 IR 5-grass pollen sublingual tablet is safe and well tolerated in children and adolescents.⁸⁴ An other multicentre trial evaluated the dose-response and tolerability of a sublingual liquid birch pollen preparation; all active treatment groups showed better responses than placebo for both primary and secondary parameters. The results indicate that, within the studied dose range, the sublingual preparation of 40,000 AUN/ml was the most optimal effective and safe dose.⁸⁵

It has been observed that some parents opt to resort to complementary medicine, such as phytotherapy. Evidence of efficacy in complementary medicine are lacking but it was recently published that a spray containing resveratrol, a natural non-flavonoid polyphenol, plus carboxymethyl-beta-glucan can relieve nasal symptoms and respiratory infections *sequelae*.⁸⁶ Further studies involving immunological parameters will be needed to confirm these observations.

Food allergy:

Dietary avoidance is the key intervention in the management of food allergy resulting in complete or almost complete resolution of symptoms.⁸⁷ Children with food allergies are at risk of inadequate nutritional intake and growth.⁸⁸ It has been observed that infants consuming cow's milk exclusion diet for cow's milk allergy had significantly higher scores of feeding difficulties and fussy eating than a control group, although they were within the normal range and growth was not affected.⁸⁹ Another study⁹⁰ evaluated the long-term effects of a cow's milk elimination diet during infancy on the eating habits and food preferences in later childhood and demonstrated it was followed-up by persistent negative eating behaviours. Nonetheless, a growing number of studies indicate that food elimination diet has no impact on growth or nutritional status of food-allergic children when diet is adequately supplemented.^{89,91,92} Reintroduction of eliminated foods needs to be carefully monitored in order to avoid failures as indicated by a retrospective study in children that underwent negative peanut food challenges but thereafter continued to avoid peanuts in a significant proportion.⁹³

Food-allergic patients at high risk of potential anaphylaxis should carry an epinephrine autoinjector (EAI) at all times. Recently the European Academy of Allergy and Clinical Immunology published the Anaphylaxis Guidelines.⁹⁴ Epipen® and Anapen® are the predominant devices used in Australasia, United Kingdom and parts of Europe. Comparing the intuitiveness of use of these devices, a greater attrition in correct use of Anapen compared to Epipen has been reported.⁹⁵ Critical errors in administration were more likely with Anapen® than Epipen®.⁹⁵ Adolescents tend to be less compliant in always carrying their EAI. In these adolescents the burden of treatment is higher as per Saleh-Langenberg et al.⁹⁶ Therefore, good adherence to self-care behaviours is significant in children and especially adolescents with food allergy and it has been exhibited that this can be supported by being member of a patient support group and having an anaphylaxis management plan.^{97,98} Moreover, the integration of validated pictograms into an anaphylaxis management plan may potentially increase comprehension of the triggers, signs, symptoms, and management of an anaphylactic reaction.⁹⁸

For the treatment of food allergy, AIT with food allergens using the subcutaneous, oral, or sublingual route has been assessed.⁹⁹ Recently, double-blind placebo controlled studies in children have shown that oral immunotherapy (OIT) with egg^{100,101} and peanut^{102,103} can be regarded as effective, and either relatively or completely safe. For children with cow's milk allergy oral immunotherapy may also be a curative and reasonably safe therapy.¹⁰⁴ A group from Finland studied the IgE and IgG4 antibody profiles against milk and milk proteins before and after OIT in relation to the clinical outcome.¹⁰⁵ They found that high IgE levels to alpha-lactalbumin, beta-lactalbumin and casein were associated with lower maintenance dose reached. Therefore, component-resolved diagnostics¹⁰⁶ before OIT might be able to help identify children with lower probability of a successful OIT and improve safety of the therapy.^{105,107} Good results have been reported by using omalizumab to facilitate simultaneous oral desensitization to multiple foods.¹⁰⁸⁻¹¹⁰ Nonetheless, there can be cases that relapse after discontinuation of omalizumab in initially successful anti-IgE-assisted oral desensitization.¹¹¹ Larger studies are needed to identify potential risk factors in such relapses. Quality of life following egg OIT in children seems to improve just a little bit if reported by parents, whereas children report a greater benefit, especially in their

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dietary restriction.¹¹² The same study revealed that allergic reactions to OIT doses impacted negatively on children's quality of life.¹¹²

Another promising, mucosal-targeting, approach in food allergy is SLIT. In 2013 the first year results of the first multicenter, randomized, double-blind, placebo-controlled clinical trial of peanut SLIT indicated a favorable safety profile, associated with modest clinical and immunologic effects.¹¹³ In 2015 the team published the long-term (three-years) effects of this intervention; peanut SLIT induced a modest level of desensitization, decreased immunologic activity over 3 years in responders, and had an excellent long-term safety profile.¹¹⁴ However, most patients discontinued therapy by the end of the third year, and only 10.8% of subjects achieved sustained unresponsiveness.

While SLIT and OIT for food allergy generally present favourable results, Narisety and colleagues¹¹⁵ thought to directly compare the safety, efficacy, and mechanistic correlates of peanut OIT and SLIT. OIT appeared far more effective than SLIT for the treatment of peanut allergy but was also associated with significantly more adverse reactions and early study drop out. While results for OIT and SLIT for food allergy appear to be promising, evidence is still overall poor and further research is needed in this field. OIT should therefore be used only in controlled clinical studies.¹¹⁶

Recently it has been shown in a double-blind, randomized, placebo-controlled study, that a 9-herb formula based on traditional Chinese medicine, is a safe herbal medication for subjects (12-45 years old) with various food allergies and shows favorable in vitro immunomodulatory effects. However, the authors could not demonstrate efficacy of the herbal formula in improving tolerance to food allergens at the dose and duration used.¹²¹

As AIT attempts to treat food-allergy, a breaking, randomized, open-label, controlled trial conducted at a single site in London was designed to determine whether the early introduction of dietary peanut could serve as an effective primary and secondary strategy for the prevention of peanut allergy.¹¹⁷ The authors demonstrated that early introduction of peanuts can significantly decrease the frequency of peanut allergy development at 5 years of age in children at high risk (severe eczema and/or egg-allergy) for this allergy and modulate immune responses to peanuts. At a later stage of this trial, a 12-month period of peanut avoidance, was not associated with an increase in the prevalence of peanut allergy among children in whom peanuts had been introduced in the first year of life and continued until 5 years of age.¹¹⁸ On the basis of these findings, a consensus communication of experts in the field suggests as an interim guidance (Level I scientific evidence) that peanut-containing products should be introduced into the diets of "high-risk" infants early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent.¹¹⁹ The clinician may perform an observed peanut challenge for those children with evidence of a positive peanut skin test response in order to determine whether they are clinically reactive before initiating at-home peanut introduction.¹¹⁹

On the other hand, a general population-based study from Perkin and colleagues could not show the efficacy of early introduction of six allergenic foods in breast-fed infants. The early introduction of all six foods was not easily achieved but was safe. The authors

raised the question whether preventing food allergy by means of early introduction of multiple allergenic foods in these breast-fed infants may depend on adherence and dose.¹²⁰

Vernal Keratoconjunctivitis:

Vernal keratoconjunctivitis (VKC) is a bilateral, chronic sight-threatening and severe inflammatory ocular disease mainly occurring in children.¹²² When inappropriately treated, it can lead to severe ocular complications. The immunopathogenetic mechanisms underlying this inflammation are unclear. Trying to have an insight into VKC immunopathology, Zicari et al.¹²³ studied the serum levels of high-mobility group box-1 (HMGB-1) and serum soluble receptor for advanced glycation end products (sRAGE) in children affected by VKC. HMGB-1 has been recently identified as an important proinflammatory mediator while sRAGE is a multiligand receptor expressed on the surface of a wide variety of cells. The engagement of RAGE with its ligands triggers rapid generation of intracellular reactive oxygen species and also leads to activation of the transcription factor NF- κ B. The study results illustrate that serum basal levels of HMGB1 and sRAGE were higher in children with VKC when compared with controls while, in patients affected by VKC no difference was detected between atopic and non-atopic, and between ANA-positive and ANA-negative children. Therefore, these results support the definition of VKC as a systemic inflammation in which HMGB1 and its soluble receptors could play a role.¹²³

Common therapies include topical antihistamines and topical steroids. The latter often provide disappointing control of the inflammatory process and may themselves lead to complications, such as glaucoma, cataract and infections.¹²⁴ Alternative therapies include immunomodulators, such as tacrolimus and cyclosporin A. Tacrolimus, has been used successfully in treating recalcitrant VKC¹²⁵ and recently Pucci et al. published that topical tacrolimus is very effective and safe in the short term for children suffering from severe VKC resistant to topical cyclosporin A.¹²⁶ Nonetheless, long-term follow up studies are needed to monitor the side effects, if any, and outcome of this intervention. An other therapeutic option investigated is the administration of omalizumab with two case reports suggesting it can be a promising option in the treatment of VKC.¹²⁷ Further studies are needed.

Chronic urticaria:

The burden of chronic urticaria in childhood seems to be inadequately perceived, which may be due to its low prevalence compared to adults.¹²⁸

Recommendations in current guidelines for the treatment of chronic spontaneous urticaria (CSU) in children are mostly based on data obtained in adults. The proposed management pathway recommends a first line treatment with non-sedating antihistamines up to a quadruple dose of the standard recommended regimen.¹²⁹⁻¹³¹ A Cochrane review indicates that several antihistamines are effective and safe in complete suppression of CSU.¹³² Rupatadine is a modern, second-generation H1-antihistamine. A new oral solution of rupatadine (1mg/ml) has recently been authorised in Europe for children aged 2-11 years with AR and/or CSU. Potter et al. studied children 2-11 years old with CSU that were administered rupatadine once daily over 6 weeks and reported it to be safe, effective and well tolerated in the relief of urticaria symptoms, while it also improved quality of life.¹³³

The application of omalizumab as a third-line option has demonstrated an additional benefit and has led to a complete relief of symptoms in almost all treated patients.¹³⁴ The recommended dose for adults is 300mg omalizumab every 4 weeks.¹³⁵ In children randomized controlled trials with omalizumab are still lacking, however, several case reports have presented a beneficial effect of omalizumab in children with CSU and solar urticaria.¹³⁶⁻¹³⁸ A team lead by Carsten Bindslev-Jensen recently published a report on 27 patients (6 children among them) with recalcitrant urticaria treated with omalizumab, proposing that the dose-interval needs to be individualized; such an approach provided a decrease in the frequency of hospital visits of the study population, and was thereby being more cost-effective for the society and convenient for the patients.¹³⁹

Hereditary Angioedema:

Hereditary angioedema (HAE) is a lifelong illness characterized by recurrent, unpredictable swelling of the skin, intestinal tract and upper airway, due to inadequate activity of the protein C1 esterase inhibitor (C1 INH).¹⁴⁰

Prevention and treatment approaches of angioedema attacks in patients with HAE include replacement of deficient C1 esterase inhibitor. Results on the subgroup of children and adolescents who participated in two placebo-controlled and two open-label extension studies using nanofiltered C1 INH demonstrate it was well tolerated, provided relief from symptoms of HAE attacks, and furthermore reduced the rate of attacks.¹⁴¹ However, questions about dosing for younger children remain. A recent study addressed the use of nanofiltered C1 INH in children 2-12 years of age and reports that treatment of a single HAE attack with C1 INH doses of 500 U (in patients 10-25 kg), 1000 U, and 1500 U (in patients >25 kg) was well tolerated.¹⁴² Pasteurized C1 INH concentrate has also been studied for treatment of acute attacks. It was effective in alleviating facial and abdominal attacks when given a dose of 20 U/kg intravenously.^{140,143} Additionally, two case reports have recently demonstrated efficacy of subcutaneous infusion of pasteurized C1 INH concentrate for acute therapy and prophylaxis of HAE in young children.^{144,145} Especially for children with restricted venous access or for those that require long-term prophylaxis at short intervals, subcutaneous C1 INH could be a promising option.

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