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Original Research

High burden of respiratory allergy in children warrants early identification and treatment with allergen immunotherapy

Eckard Hamelmann [a,*], Péter Csonka [b,c], Graham Roberts [d,e,f], Christian Vogelberg [g], Ewa Cichocka-Jarosz [h], Jocelyne Just [i,j,k], Miloš Jeseňák [l]

[a] Department of Paediatrics, Children's Center Bethel, University Bielefeld, Bielefeld, Germany
[b] Tampere Center for Child, Adolescent and Maternal Health Research, Tampere University and Tampere University Hospital, Tampere, Finland
[c] Terveystalo Healthcare Oy, Tampere, Finland
[d] The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK
[e] NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[f] University of Southampton Faculty of Medicine and University Hospital Southampton, Southampton, UK
[g] Department of Pediatrics, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[h] Department of Pediatrics, Pulmonology, Allergology and Dermatology Clinic, Jagiellonian University Medical College, Kraków, Poland
[i] Unité d'Allergologie, Hôpital Américain de Paris, Neuilly sur Seine, France
[j] Sorbonne Université, Paris, France
[k] CRESS, Inserm, INRAE, HERA Team, Université Paris Cité, France
[l] Department of Pediatrics and Department of Clinical Immunology and Allergology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, University Hospital in Martin, Martin, Slovakia

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ABSTRACT

Respiratory allergy often begins in childhood and most commonly manifests as allergic rhinitis (upper airways) and/or asthma (lower airways). Children with upper respiratory allergy often suffer from coexisting asthma, and other comorbidities ranging from gastrointestinal disorders to emotional/mental health disorders. Consequently, the disease burden is considerable and profoundly impacts a child's daily life.

Early identification and appropriate management are important to reduce disease burden, lower the risk of disease progression and additional comorbidities, and protect the child's future well-being. A window of opportunity for halting disease progression may open in the early stages of allergic disease and underlines the importance of early diagnosis and treatment of children at risk. This review offers advice on identifying children with a high disease burden who would benefit from early intervention.

Allergen immunotherapy (AIT) modifies the cause of respiratory allergy and prevents disease progression. In clinical practice, AIT could be considered as an early treatment for eligible children, to achieve long-term symptom control and disease modification.

1. Introduction

1.1. The epidemiology of respiratory allergy in children

Respiratory allergy refers to an intolerance of the immune system in sensitised individuals to otherwise harmless inhaled substances (allergens) present in the environment [1,2]. The airway inflammation associated with respiratory allergy can affect the upper airways (as allergic rhinitis [AR] or allergic rhinoconjunctivitis [ARC]) as well as the lower airways (as asthma) [1]. The most common respiratory allergens for AR include grass, tree and ragweed pollen, house dust mite (HDM), and animal dander [2]. Respiratory allergy is a highly prevalent disease and evidence suggests that the prevalence is increasing in children [3], although recent trends show variation between regions [4]. Children suffering from respiratory allergy often have co-existing conditions, as illustrated by the EuroPrevall-iFAAM birth cohort study – of 5572 school

Abbreviations: AD, atopic dermatitis; AIT, allergen immunotherapy; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; EAACI, European Academy of Allergy and Clinical Immunology; HDM, house dust mite; IgE, immunoglobulin type E; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

* Corresponding author. Department of Paediatrics, Children's Center Bethel, University Bielefeld, Bielefeld, Germany.
E-mail addresses: eckard.hamelmann@uni-bielefeld.de (E. Hamelmann), peter.csonka@tuni.fi (P. Csonka), g.c.roberts@soton.ac.uk (G. Roberts), Christian.Vogelberg@ukdd.de (C. Vogelberg), mijarosz@cyfronet.pl (E. Cichocka-Jarosz), jocelyne.just@inserm.fr (J. Just), jesenak@gmail.com (M. Jeseňák).

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children (aged 6–10 years), 13.3 % had AR, 8.1 % had asthma, 12.0 % had eczema, and 7.0 % had allergic multimorbidity (at least two allergic diseases) [5]. Within respiratory allergy, AR is considered an important risk factor for the development of asthma; childhood AR is associated with an up to 7-fold increased risk of developing asthma (versus no childhood AR) [6,7]. Indeed, it is estimated that 49.5 % of children with AR also have asthma [8], and more than 60 % of people with asthma diagnosed in childhood have concomitant AR [9]. Data from birth cohort studies suggest that children with perennial AR may be more prone to developing asthma than those with seasonal AR. For example, the Pollution and Asthma Risk: an Infant Study (PARIS) cohort showed that the risk of developing asthma was highest in children who were strongly sensitised to HDM at 8 or 9 years of age compared to children with other sensitisation profiles, including those with a general sensitisation to grass pollen [10]. In addition, the German Multicentre Allergy Study cohort reported that early sensitisation to perennial allergens (e.g., to HDM/animal dander in the first 3 years of life) was associated with a loss of lung function when the child was of school age, whereas sensitisation to seasonal allergens (e.g. birch, grass) had no such effect on lung function [11].

1.2. The progression of respiratory allergy in children

Respiratory allergy is a chronic, often progressive, disease that usually begins in childhood. Evidence indicates that atopic dermatitis (AD), immunoglobulin type E (IgE)-mediated food allergy, asthma, and AR have common genetic predispositions (i.e., atopy) and environmental risk factors, as well as shared pathophysiology with dysregulation of the immune system and skin barrier defects [12]. Studies have shown that children with comorbid manifestations in early childhood (e.g., eczema, wheezing, food allergy) have an increased risk of developing AR and asthma [13]. For example, the risk of developing AR is increased by 4-fold in children with early-onset AD (<1 year of age) versus no AD; the corresponding increased risk for developing asthma is 3.4-fold [14]. However, symptom development, sequence, and progression of allergic diseases in children can be heterogenous in clinical practice, with different disease phenotypes leading to allergic multimorbidity [15].

Regardless of the exact course of progression, various factors play a role in the development of respiratory allergy. Skin barrier defects are central to the development of AD, and enhancing both food and respiratory allergen sensitisation by promoting the penetration of antigens (i.e., allergens) and activation of immune responses [12,16]. The epithelial barriers, such as the skin and the respiratory mucosa, can be damaged by environmental pollutants, resulting in local inflammation and further barrier disruption [17]. Genetic predisposition is an additional important risk factor for allergy development (including multimorbidity) in children [18].

1.3. The burden of upper respiratory allergy in children

Upper respiratory allergy has a considerable negative impact on many aspects of a child's quality of life (e.g., sleep, social/physical engagement, performance at school) [19,20]. This burden of disease can be increased by the presence of comorbid allergic diseases, such as AD and asthma, which are strongly correlated with AR [20]. The true prevalence and associated burden of upper respiratory allergy is most likely underestimated in children; common colds are frequent and often accompanied by symptoms similar to AR, meaning that the underlying AR may not be diagnosed, or it may be misdiagnosed [2,21,22]. Self-management of AR symptoms, using over-the-counter medications (e.g., antihistamine and intranasal corticosteroids) without guidance from a medical professional, not only results in the risk of side effects (e.g., rhinitis medicamentosa [2]), but also represents a missed opportunity for a specific diagnosis, adequate treatment to control the symptoms, and referral to specialists if necessary [23,24]. Altogether, the burden of upper respiratory allergy and inadequate management can influence a child's future development.

Early identification and treatment of upper respiratory allergy in children is important to ameliorate the burden of disease, lower the risk of disease progression (especially from AR to asthma), and reduce the development of additional comorbidities. This review: 1) summarises the clinical evidence for the burden of upper respiratory allergy in children (identified through targeted literature searching); 2) highlights the value of timely and early management; 3) emphasises the importance of clinical management for upper respiratory allergy through early identification of children with a high disease burden and highlighting the clinical relevance of applying allergen immunotherapy (AIT) in the treatment approach.

2. The negative impact of upper respiratory allergy on quality of life

Fig. 1 illustrates the many ways in which upper respiratory allergy can affect children's quality of life.

2.1. Comorbidities

AR is a chronic inflammatory disease of the upper airways. A range of different comorbidities impacting multiple organ systems can develop in children with upper respiratory allergy (Fig. 2), all of which can further increase the burden of disease [19,21,25,26].

AD and asthma, in particular, are among the most common comorbidities, reported in ≥20 % of children with AR [8,25]. Evidence suggests that AR can be underdiagnosed in children with asthma [29], and that AR can impact the severity and control of asthma [30]. Consequently, accurate diagnosis and appropriate treatment of AR in children are important factors. Upper airway problems are also common in children with AR [21]. In a paediatric survey, sinus problems were reported for 43 % of children with AR and 18 % underwent removal of tonsils and/or adenoids [19]. In addition, children with AR (triggered by pollen, in particular) can be affected by pollen–food allergy syndrome, which causes oral pruritus upon ingestion of specific raw food items (e.g., apple or peach) [21]. The wide range of other medical conditions that can develop in children with AR emphasises the importance of assessing comorbidities in these individuals.

2.2. Restriction of daily activities

The nasal and ocular symptoms of upper respiratory allergy affect many aspects of typical daily life for children. For example, limitations in outdoor activities, playing with friends, and in organised sporting activities are approximately 3–5 times more frequent in children with respiratory allergy than in children without respiratory allergy [19]. Furthermore, allergic children show a lower preference for participating in certain activities (physical, social, skill-based, etc.) than their non-allergic peers [31]. Since AR is often associated with other atopic diseases [25], such as AD and/or asthma, children may also experience activity restrictions and social isolation driven by these comorbidities [32,33].

2.3. Sleep disturbance

Nasal congestion, which often occurs in upper respiratory allergy, is a common cause of mouth breathing that results in snoring in allergic children [19]. Mouth breathing may lead to dental malocclusion, which is increased in children with upper respiratory tract disorders, such as AR and sinusitis [34]. Furthermore, AR is prevalent in children with sleep-disordered breathing (e.g., obstructive sleep apnoea) [35]. Other sleep disturbances include, difficulty falling asleep, reduced duration of sleep, nocturnal awakening, and poor sleep quality [19,20]. Sleep problems have been reported among the main reasons for seeking medical care in 65.8 % of children with AR triggered by HDM [36].

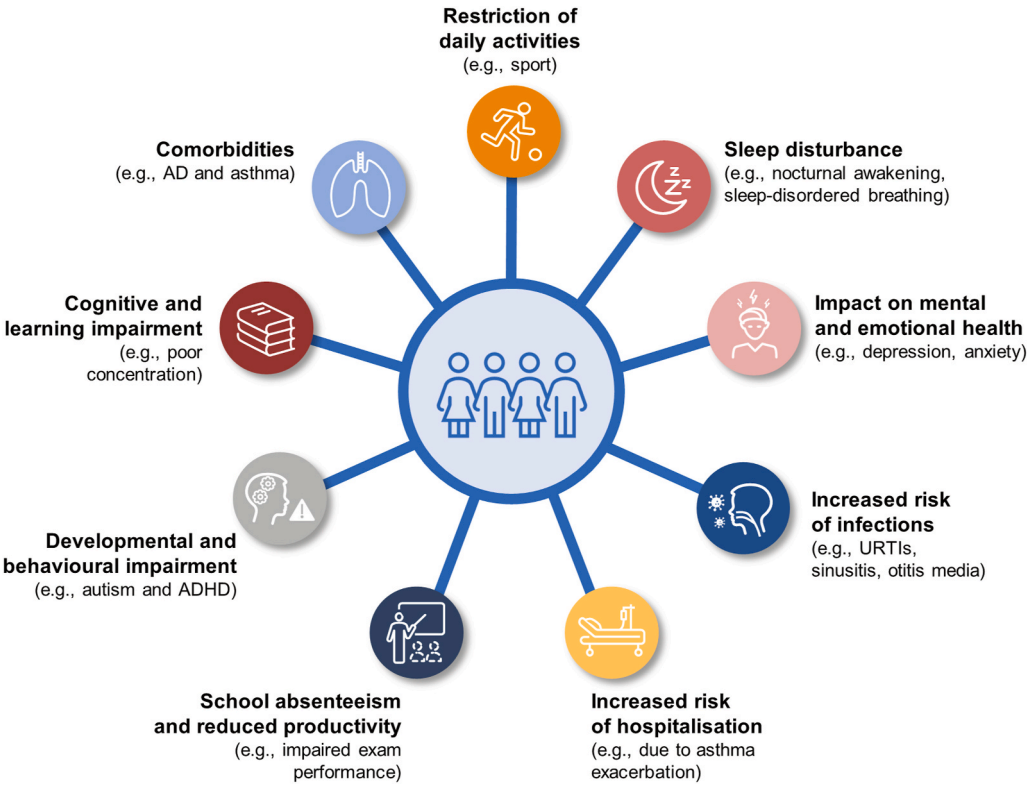

Fig. 1. Factors contributing to the burden of upper respiratory allergy in children. AD, atopic dermatitis; ADHD, attention-deficit hyperactivity disorder; URTI, upper respiratory tract infection.

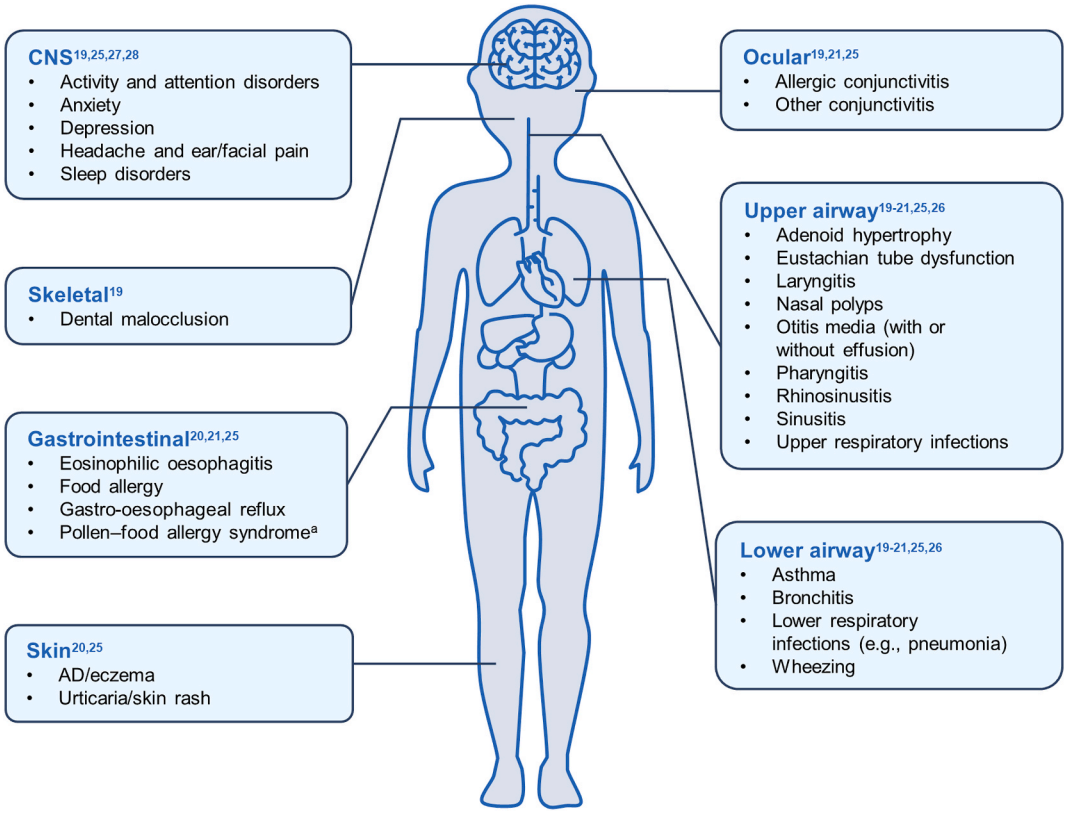

Fig. 2. Comorbidities associated with upper respiratory allergy in children. [a]Also known as oral allergy syndrome. AD, atopic dermatitis; CNS, central nervous system.

Sleep problems can act as a mediator between allergic disease and psychological distress, highlighting the importance of assessing sleep health in children [37].

2.4. Cognitive and learning impairment

The negative effect of upper respiratory allergy on sleep can cause daytime fatigue which, subsequently, impacts concentration and cognitive functioning [19,38]. Studies have shown that children with allergies can experience impaired performance at school and difficulties with learning [19,39], and that the learning impairment is worse in children with poor symptom control [20]. Learning can also be negatively impacted by the use of sedating symptom-relieving medication [39].

2.5. School absenteeism and reduced productivity

AR symptoms and associated sleep disruptions can lead to missed school days. One study reported that 32 % of children with AR were absent from school at least once per month because they were unwell versus 11 % of children without AR [20]. Even when children are in school, AR symptoms can impair their productivity [19,20], which can have implications for peer relationships and future employment trajectories [40]. Furthermore, students (aged 15–17 years) with seasonal upper respiratory allergy who dropped one or more grades between summer and winter examinations were more likely (almost 1.5-fold) to have been experiencing allergic symptoms during the summer assessments than students with unchanged/improved grades [39].

2.6. Increased risk of infections

Based on insights into the mechanisms causing allergy [41], respiratory allergy is associated with impairment of the airway epithelial barrier function and impaired antiviral immunity, allowing allergens, bacteria, viruses and pollutants to penetrate the airways and cause respiratory infections. Consequently, the occurrence of frequent and prolonged upper respiratory tract infections (of rhinovirus aetiology or respiratory syncytial virus, in particular) may be a potential indicator of respiratory allergy in childhood. An epidemiological study has shown that atopic children were more susceptible to viral respiratory infections than non-atopic children, with the highest susceptibility in those aged 2–5 years [42]. Children with AR can also suffer from other infectious manifestations, such as bronchitis, pneumonia, and otitis media [43].

2.7. Increased risk of hospitalisation

Since AR and asthma often co-exist in children, asthma exacerbation is a common cause of hospital admission in children with AR, and can be triggered by exposure to natural allergens (e.g., grass and birch pollen) [44,45] and to viruses [44]. Children with asthma and comorbid AR are almost 3-fold more likely to have poor asthma control than children without comorbid AR [46]. In a population-based cohort study of more than 9000 children with asthma, children with comorbid AR incurred higher prescription costs, attended more general practitioner appointments, and experienced more hospitalisations for asthma than children without AR [47].

2.8. Impact on mental and emotional health

The quality-of-life burden of upper respiratory allergy in children can also negatively impact mental health. Children with allergic multimorbidity experience more emotional problems, including poorer emotional health, compared with children without allergic diseases [20,48]. In a paediatric survey among children aged 6–15 years, having AR was associated with 2.14 days of poor emotional health in the previous month, compared with 0.62 days for not having AR [20]. In addition, a causal role of AR in the development of depressive mood has been demonstrated in children and pre-adolescents [27,49]; the presence of anxiety was also associated with depressed mood in pre-adolescents [27].

2.9. Developmental and behavioural impairment

Evidence suggests that children with allergic diseases have a higher level of hyperactivity and conduct problems than children without these diseases [48]. In addition, atopic disease in childhood (especially allergic multimorbidity) has been associated with an increased risk of developing attention-deficit hyperactivity disorder and, possibly, autistic spectrum disorder [28]. Both genetic and inflammatory mechanisms have been suggested to play a role in the development of behavioural impairments in children with respiratory allergy [28].

3. Reducing the burden of disease – the importance of managing upper respiratory allergy early in life

With the aim of reducing the burden of disease in children, early diagnosis and intervention is needed to achieve optimal symptom control, as well as to prevent further disease progression [50,51]. It has been proposed that a window of opportunity for preventing disease progression and reducing the burden of disease may exist, especially in children at an early stage of allergic disease [51]. Key considerations for the diagnosis and management of upper respiratory allergy in children are summarised in Box 1.

3.1. Diagnosis

A diagnosis of upper respiratory allergy in children is based on [22,26]:

- a clinical history of recurrent upper airway symptoms in association with allergen exposure (seasonal and/or perennial)
- sensitisation to the suspected allergen is confirmed by the results of appropriate diagnostic testing via skin prick tests and/or testing for allergen-specific IgE using a blood sample
- supportive findings from physical examination (note: abnormalities may not always be present, e.g., outside the pollen season).

Pollen from grass and trees (especially birch), HDM, and animal dander are among the most common respiratory allergens for allergic children, and can vary according to geographical location (e.g., pollen) [50,54]. Diagnostic testing should, therefore, consider the most prevalent allergens (seasonal and perennial) in the local area, to identify the causal allergen(s) responsible for the respiratory symptoms [50]. This is important for two reasons – to support clinical decision making, and to recognise the evidence for an increased risk of asthma and impaired lung function with perennial versus seasonal allergens [10,11].

3.2. Initial treatment

International guidelines and expert opinions recommend second-generation antihistamines and/or intranasal corticosteroids, or a fixed combination of both, for first-line treatment of children with upper respiratory allergy [21,22,50,52]; these medications provide short-term symptomatic relief only [22,50].

3.3. Allergen immunotherapy

AIT may be considered for children who continue to experience burdensome symptoms that impact quality of life despite regular use of symptom-relieving pharmacotherapy [50], and/or children who experience side effects of current medications. Currently, AIT is the only treatment for respiratory allergy that targets the underlying cause of

Box 1
Clinical considerations for the management of upper respiratory allergy in children.

- Upper respiratory allergy is diagnosed based on a clinical history of upper airway symptoms in association with allergen exposure.[22] It is confirmed by performing a skin prick test or by measuring allergen-specific IgE in a blood sample.[22] The diagnosis can be supported by physical examination.[22]
- Avoiding the triggering allergen (e.g., pollen, HDM, or animal dander), where possible.
- First-line treatment with intranasal corticosteroids and/or non-sedative antihistamines, or a combination of both, can provide short-term symptom relief for children with upper respiratory allergy.[21,22,50,52]
- Long-term symptom control is an important treatment goal in children to reduce the burden of disease and the risk of disease progression.[50]
- AIT can provide long-term, sustained symptom control, and is the only disease-modifying treatment that can alter the course of allergic disease and prevent the development of asthma.[50,53]
- AIT should be considered in all eligible children when symptoms continue to impact on quality of life and daily activities despite treatment with symptom-relieving pharmacotherapy,[49] and/or the child experiences burdensome side effects with current medications. It may also be considered in children with less severe AR to take advantage of the long-term and disease-modifying effects of AIT on AR and asthma.[50]
- AIT is available as sublingual immunotherapy (SLIT) tablets or drops, or as subcutaneous injections (SCIT).[50]

AIT, allergen immunotherapy; AR, allergic rhinitis; HDM, house dust mite; IgE, immunoglobulin type E.

allergic disease by providing repeated standardised doses of relevant allergens [50]. Therefore, AIT not only alleviates symptoms through the induction of immunological tolerance to the causative allergen, but also has the potential to halt the progression of allergic disease (e.g., prevents worsening of symptoms, new sensitisations, and asthma onset) [22,50,55]. According to guidelines from the European Academy of Allergy and Clinical Immunology (EAACI), a 3-year course of continuous AIT is recommended to achieve long-term symptom control and disease-modifying effects in children with respiratory allergy [21,50]. Given the potential for long-term benefits, guidelines suggest that AIT may also be considered in children at early stages of allergic disease if they wish to take advantage of its ability to alter the natural course of disease [50]. Support for potential disease modification with AIT comes from clinical studies in children with seasonal AR or ARC (due to grass and/or birch) suggesting a preventative effect of AIT on disease progression by reducing the risk of developing asthma symptoms or requiring asthma medication use [50,55,56]. Furthermore, in an economic modelling analysis, initiation of AIT in early childhood has been associated with a clinically meaningful reduction in the risk of asthma (and with lower healthcare costs) [57]. The early preventative effects of AIT are relevant to consider given the possibility that many children have bronchial hyperresponsiveness in the absence of wheezing [58]. AIT may have the added benefit of improving airway epithelial barrier function by reducing the risk of respiratory tract infections requiring antibiotics [43,59]. There is also mounting evidence to suggest that AIT specific to aeroallergens, particularly HDM, can also have a beneficial clinical effect for children with AD through improvements in disease severity and in quality of life [60].

3.3.1. The growing evidence for allergen immunotherapy in children with upper respiratory allergy

Various systematic reviews and meta-analyses of the clinical evidence for AIT, including studies in children, support the clinical efficacy for certain indications, allergens, and ages [61,62]. However, heterogeneity between studies precludes the recommendation of a class effect for AIT and, therefore, it is important to evaluate the clinical evidence in children from a product-specific perspective [53,61]. Table 1 summarises clinical trials of different AIT products that included paediatric populations; the data from some of these trials have been used to inform clinical guidelines. The EAACI guidelines for AIT include a moderate recommendation for the use of grass subcutaneous immunotherapy (SCIT) in children with seasonal AR, based on small randomised controlled trials with mixed populations (adults and children), and a randomised, open-label trial of grass and/or birch SCIT in children [53,56,86,87]. However, high-quality specific data for SCIT in treating perennial AR (i.e., due to HDM, for example) in children are lacking [50,53,61]. In comparison, there is robust (and mounting) evidence from randomised, double-blind, placebo-controlled trials confirming the efficacy and safety of sublingual immunotherapy (SLIT)-tablets to treat children and adolescents with upper respiratory allergy due to various allergens – grass, tree, ragweed, and Japanese cedar pollen, and HDM (Table 1). Of all studies, the two paediatric trials of SLIT-tablets - TT-06 and MT-12 - are the most recent trials to provide evidence for AIT in children with AR due to tree pollen and HDM, respectively [69,70,78,79].

Ideally, AIT should be initiated early in the disease course in children with AR, and multiple factors should be considered when making the

Table 1
Randomised, double-blind, placebo-controlled trials including paediatric populations that investigated the efficacy and safety of AIT for the treatment of upper respiratory allergy due to various seasonal and perennial allergens.

Allergen	AIT product	Trial identifier	Randomised (N)	Age (years)	Reference(s)	Included in EAACI[a]/ S2K[b] guidelines
SLIT-tablets						
Grass	SQ grass SLIT-tablet (75,000 SQ-T)	GT-12 (NCT00408616)	253	5–16	Bufe et al. (2009) [63]	Both[c]
		P05239 (NCT00550550)	345	5–17	Blaiss et al. (2011) [64]	Both[c]
		P08067 (NCT01385371)	1501	5–65	Maloney et al. (2014) [65]	S2K only
		GAP (NCT01061203)	812	5–12	Valovirta et al. (2018) [55]	Both[c]
	5-grass SLIT-tablet (300 IR)	NCT00409409	278	5–17	Wahn et al. (2009) [66]	Both[c]
	Grass allergoid SLIT-tablet	None[d]	48	4–14	Caffarelli et al. (2000) [67]	EAACI only[c]
Tree[e]	SQ tree SLIT-tablet (12 SQ-Bet)	TT-04 (EudraCT 2015-004821-15)	634	12–65	Biedermann et al. (2019) [68]	S2K only
		TT-06 (NCT04878354; EudraCT: 2020-004372-17)	952	5–17	NCT04878354 [69] EudraCT: 2020-004372-17 [70]	S2K only
Ragweed	SQ ragweed SLIT-tablet (12 SQ-Amb)	P008 (NCT02478398)	1025	5–17	Nolte et al. (2020) [71]	S2K only
Japanese cedar	JC pollen SLIT-tablet (2,000, 5,000, and 10,000 JAU)	JapicCTI-142579	1042	5–64	Gotoh et al. (2019) [72] Yonekura et al. (2021)[f] [73]	No
HDM	SQ HDM SLIT-tablet (12 SQ-HDM)	P001 (NCT01700192)	1482	≥12	Nolte et al. (2015) [74]	Both[c]
		TO-203-3-2 (JapicCTI-121848)[g]	946	12–64	Okubo et al. (2017) [75]	Both[c]
		TO-203-3-3 (JapicCTI-152953)[h]	458	5–17	Masuyama et al. (2018) [76]	S2K only
		MT-12 (NCT04145219; EudraCT 2019-000560-22)	1458	5–11	NCT04145219 [77] EudraCT: 2019-000560-22 [78]	S2K only
	HDM SLIT-tablet (300 IR)	EudraCT: 2014-004223-46 NCT02443805	1607	12–65	Demoly et al. (2021) [79]	S2K only
		JapicCTI-152981	438	5–16	Okamoto et al. (2019) [80]	S2K only
		JapicCTI-121917[i]	968	12–64	Okamoto et al. (2017) [81]	Both
SLIT-drops						
Grass	Grass SLIT-drops	None[e]	97	3–14	Rolinck-Werninghaus et al. (2004) [82]	No
	Grass SLIT-drops	None[e]	60	6–18	Stelmach et al. (2012) [83]	EAACI only[c]
Birch, hazel, alder	Birch SLIT-drops	None[e]	98	5–14	Valovirta et al. (2006) [84]	EAACI only[c]
Japanese cedar	JC pollen SLIT-drops	JapicCTI-101259	531	12–64	Okamoto et al. (2015) [85]	EAACI only
SCIT						
Grass	6-grass pollen allergoid	None[e]	45	12–43	Bousquet et al. (1987) [86]	EAACI only[c]
	4-grass pollen extract	None[e]	33	9–46	Weyer et al. (1981) [87]	EAACI only[c]

AIT, allergen immunotherapy; ARC, allergic rhinoconjunctivitis; AR/C, allergic rhinitis/rhinoconjunctivitis; EAACI, European Academy of Allergy and Clinical Immunology; GAP, GRAZAX Asthma Prevention; HDM, house dust mite; JC, Japanese cedar; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy. The table lists randomised, double-blind, placebo-controlled trials of AIT in AR/C that recruited paediatric populations, including trials mentioned in the EAACI and German S2K guidelines, as well as recently completed trials and trials that were not included in the aforementioned guidelines (sourced by manual searching). The following types of AIT trials were excluded: non-randomised/non-blinded trials, real-world evidence trials, trials in subjects with asthma or where the primary outcome was an asthma outcome or inflammatory marker, trials exploring the efficacy of AIT in primary care clinics and specialist centres, and trials including adults only or where the age group was not defined.

[a] Supported by the EAACI guidelines on AIT for ARC [53], and the EAACI AIT users guide [50].
[b] Guideline on AIT prepared and financed by the German Society of Allergology and Clinical Immunology (DGAKI) [61].
[c] Evidence was used to support the formal EAACI recommendation for AIT as published in the EAACI guidelines [53].
[d] No trial identifier (ClinicalTrials.gov or EudraCT databases) was stated in the publication.
[e] Birch homologous group (alder, birch, hazel, hornbeam, oak).
[f] 5,000 JAU dose.
[g] 6 SQ-HDM or 12 SQ-HDM dose.
[h] 6 SQ-HDM dose.
[i] 300 IR or 500 IR dose.

treatment decision: age of the child (aged ≥5 years); causative allergen; severity of symptoms and their impact on daily life; duration of disease and previous treatment with symptom-relieving medication; and existing comorbidities [50,53].

Although AIT has been demonstrated to be efficacious and well tolerated in children, there remains a large proportion of children suffering from upper respiratory allergy [50] worldwide [88], indicating that AIT is still underused in the paediatric population [43]. A real-life study has shown that, in children, AIT is often introduced late in the disease course when AR is considerably impacted by comorbidities [25]. Restricted access to AIT, reimbursement challenges, and a lack of agreed referral pathways between primary and specialist care, may partly account for the delayed and limited use of AIT [89]. Additionally, an Italian questionnaire-based study has reported insufficient knowledge among paediatricians of the positioning of AIT in treatment guidelines; approximately half perceive AIT as an adjunctive treatment when symptom-relieving treatment fails [90]. Consequently, to ensure timely access to AIT for eligible children, it is essential to encourage the early identification of children with a high burden of disease, and to educate clinicians, children, and their caregivers about the available treatment options. Ideally, AIT initiation should occur prior to the development of comorbidities, such as asthma, in high-risk children with AR (e.g., children with allergic manifestations in early childhood and a parental history of allergy/asthma). However, children with AR and well-controlled asthma can also be considered for treatment with AIT, in light of the evidence showing a reduction in asthma symptoms and asthma medications, in addition to the clinical benefits for AR [50], as can children with partially-controlled asthma.

4. Early identification of children with a high burden of disease

Clinicians should consider a range of factors when evaluating the burden of upper respiratory allergy in children (Fig. 3). Together with questions addressing the type and severity of symptoms, and the use of symptom-relieving medications, it is important to ask for general information about symptom-related restrictions on the child's daily life (on sleep, activities, etc.), to establish a full picture of the disease burden. Encouraging children and/or their caregivers to document symptoms in a diary can considerably aid the process of information gathering.

Poor symptom control negatively impacts a child's quality of life [20]. Therefore, in clinical practice, early identification of children with a high burden of upper respiratory allergy is important to: 1) obtain a timely diagnosis; 2) identify the causal allergen and provide optimal management with symptom-relieving medication; 3) allow consideration of AIT earlier in the disease course to relieve the burden and provide long-term reductions in symptoms and medication use, and disease-modifying effects [50,51]. Recognising that confounding factors (e.g., wheezing, respiratory tract infections) can overshadow the identification and burden of upper respiratory allergy, it is also important to ask the child/caregiver about the presence of other comorbidities (see Fig. 3) [21]. If more advanced objective procedures are required to confirm or exclude a diagnosis of upper respiratory allergy (e.g., nasal provocation testing or nasal cytology), or of comorbidities, such as asthma (e.g., spirometry, fractional exhaled nitric oxide testing, or impulse oscillometry), the child should be referred for specialist care.

5. Conclusions

Upper respiratory allergy can significantly affect children's lives and may have ramifications for their future development and life potential. However, the burden of upper respiratory allergy in children is often underestimated and/or addressed too late. Therefore, in routine clinical consultations with children and their caregivers, it is important to pose appropriate questions that will draw out the essential information needed to form a detailed picture of the impact that upper respiratory allergy and comorbidities have on the quality of life of the child.

Early identification of children with upper respiratory allergy and a high burden of disease (i.e., children who would benefit from optimised management of their condition) is key to providing timely diagnosis and appropriate treatment to obtain symptom control. In clinical practice, it is relevant to consider causal treatment with AIT in eligible children to maximise the long-term benefits of symptom reduction and prevention of disease progression (with associated potential economic savings). The clinical evidence for AIT in children is growing, and the majority of randomised, placebo-controlled trials in paediatric populations have been conducted with SLIT-tablets. Eligible children should receive AIT early in the disease course when a potential window of opportunity to modulate the allergic disease and build tolerance to the causative allergens exists.

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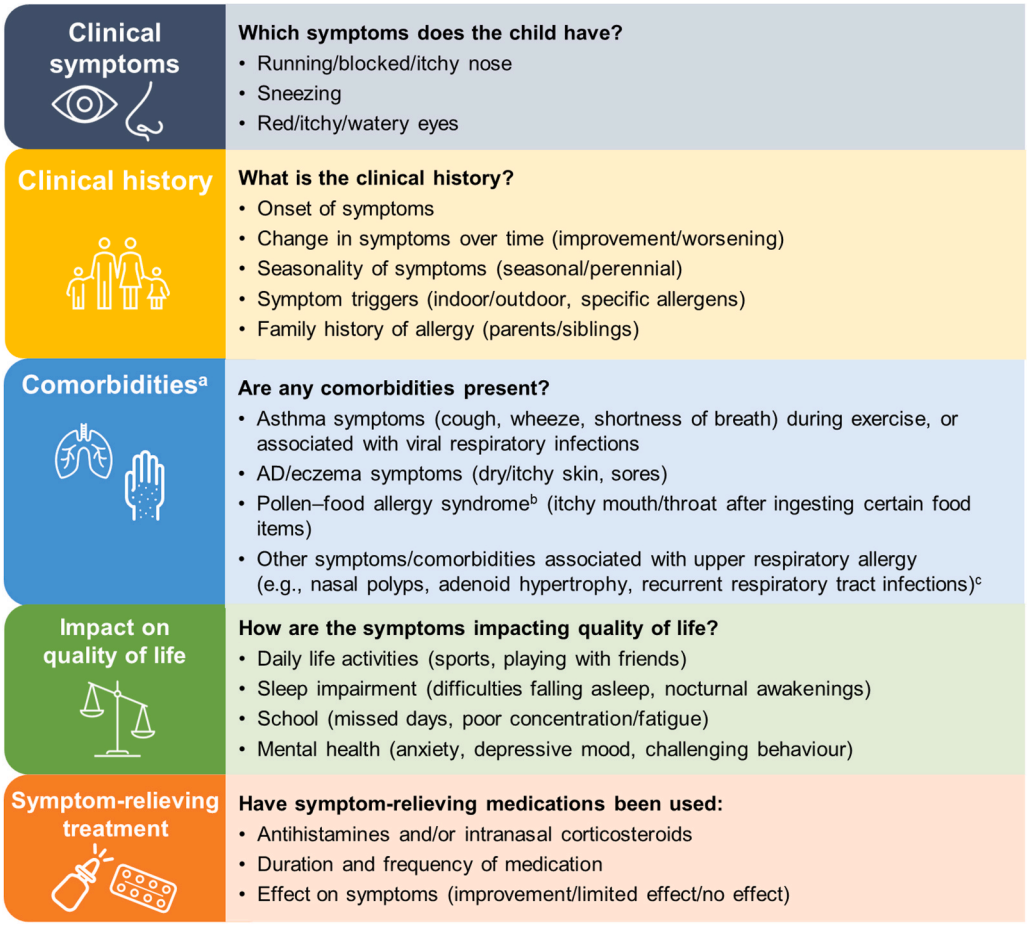

Fig. 3. Key factors to consider when identifying children with a high burden of upper respiratory allergy. [a]Consider conducting diagnostic tests where necessary (e.g., spirometry); [b]Also known as oral allergy syndrome; [c]Evaluate possible association of other symptoms/allergic diseases with upper respiratory allergy. AD, atopic dermatitis.

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Data availability statement

The information presented in this review has been gathered from the existing literature that is available in the public domain, and evaluated by the authors.

Educational aims

The reader will come to appreciate:

- that upper respiratory allergy can have a considerable negative impact on the daily lives and future development of children
- that upper respiratory allergy in children is often associated with multiple comorbidities further adding to the long-term burden of the disease
- that early identification of children with upper respiratory allergy and a high burden of disease is key to timely diagnosis, to optimal treatment, and to reduce the risk for comorbidities
- that, in clinical practice, AIT should be considered earlier in the disease for eligible children, to achieve long-term symptom control and disease modification.

Future research directions

The potential benefits associated with avoiding the complications of severe upper respiratory allergy are wide-ranging. Consequently, an important question for further exploration is the age at which AIT should be initiated to prevent the progression of respiratory allergy. Additional studies are required to investigate the ideal window of opportunity for starting treatment with AIT in order to achieve maximal disease-modifying effect – how early should AIT be initiated?

Other additional evidence gaps recommended for further investigation are summarised below:

- more mechanistic evidence on how AIT could improve asthma control (also, during periods of respiratory infection)
- more data on the overall cost of atopic diseases and comorbidities – could AIT reduce the direct and indirect costs associated with atopic diseases?
- identification of biomarkers for monitoring the success of AIT treatment
- more data on the additional effects of AIT (e.g., reduced frequency of infections, decreased use of antibiotics, avoiding disease progression, prevention of new allergen sensitisations, renewal of the epithelial barrier, etc.).

CRediT authorship contribution statement

Eckard Hamelmann: Writing – review & editing, Supervision, Conceptualization. **Péter Csonka:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Graham Roberts:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Christian Vogelberg:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Ewa Cichocka-Jarosz:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Jocelyne Just:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Miloš Jeseňák:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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