Journal of Asthma and Allergy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Diagnosis and Management of Allergic Rhinitis in Asthmatic Children

Laura Tenero[1], Rachele Vaia[2], Giuliana Ferrante[1], Matteo Maule[3], Laura Venditto[1], Giorgio Piacentini[1], Gianenrico Senna[2,3], Marco Caminati[3]

[1]Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Clinic, University of Verona, Verona, Italy; [2]Allergy Unit and Asthma Center, Verona University Hospital, Verona, Italy; [3]Department of Medicine, University of Verona, Verona, Italy

Correspondence: Marco Caminati, Department of Medicine, University of Verona, Piazzala L.A. Scuro, 10, Verona, 37134, Italy, Email marco.caminati@univr.it

Abstract: Allergic rhinitis (AR) is a common upper airways inflammatory condition especially in paediatric population; its burden potentially impacts on quality of life, quality of sleep and daily performance, which can be difficult to perceive but not less relevant in the middle-long term. The present review aims to provide an updated overview on AR epidemiology, diagnosis and with a special focus on its connections with bronchial asthma. In fact, when considering asthmatic pediatric population, AR is probably the most important risk factor for asthma onset and the most impactful extra-bronchial determinant of asthma control. Under this perspective, allergen immunotherapy (AIT) should always be considered in the light of a precision medicine approach. In fact, AIT does represent a unique opportunity to specifically interfere with AR immunological background, improve both AR and bronchial asthma control and prevent allergic disease evolution. Verifying the patient's eligibility to that option should be considered as a priority for every physician managing children suffering from AR, especially when associated with bronchial asthma.

Keywords: asthma, asthma control, rhinitis, immunotherapy, personalized medicine

Allergic Rhinitis: Not a Trivial Issue

Rhinitis is characterized by typical pattern of nasal symptoms, including nasal congestion/obstruction, rhinorrhoea, sneezing and pruritus, expressing the underlying inflammation and/or dysfunctional nasal mucosa.[1]

Three distinct rhinitis subgroups, or phenotypes, are widely accepted: allergic rhinitis (AR), infectious rhinitis, and non-allergic, non-infectious rhinitis (NAR). However, overlapping or combined phenotypes may co-exist in several patients and present a dynamic evolution over time.[1,2]

Allergic rhinitis (AR) clinically expresses an immunoglobulin E (IgE)-mediated reaction to allergens that occurs starting from the nasal mucosa.[3,4] According to ARIA (Allergic Rhinitis and its Impact on Asthma) consensus, allergic rhinitis can be classified as intermittent or persistent, following symptoms duration, and mild–moderate or severe when taking into account symptoms severity. The environmental triggers causing allergic rhinitis are represented by airborne proteins from pollens, house dust mites (HDM), insect faeces, animal dander, and molds.[5] The disease clinical expression is the result of a complex immunological cascade and biochemical events. The inhaled allergens are firstly processed by the antigen-presenting cells (APCs) in the nasal mucosa and presented to CD4+ T lymphocytes. The last produce so-called T2 cytokines (eg, IL-3, Il-4, IL-5, IL-13, granulocyte-macrophage colony-stimulating factor), which lead to differentiation of B lymphocytes to plasma cells, and subsequently to the production of antigen-specific IgE that bind to IgE receptors (FcERI) on the surface of mast cells and basophils. When allergen exposure occurs again, allergenic peptides are recognized by specific IgEs bounding mast cells or basophils. As an immediate further step, the cross-linking of IgE molecules activates an intracellular signalling cascades leading to the degranulation of bioactive mediators (eg, histamine, leukotrienes, prostaglandins, platelet activating factor).[2,6] Delayed or persistent nasal inflammation is sustained by the release of chemokines and other chemo-attractants that drive Th2 cells, activated eosinophils, and mast cells to migrate into the nasal epithelium where they release additional mediators that prolong allergic inflammation.[7] The

Received: 1 September 2022
Accepted: 19 December 2022
Published: 5 January 2023

complex immunological background sustains the potential systemic relevance of the inflammation underlying allergic rhinitis, and accounts for the role of AR as the major risk factor for bronchial asthma, as discussed below.

The prevalence of AR ranges from 10% to 30% worldwide,[8] and approximately 400 million people are affected by the disease.[9] It is a widespread pathologic condition with significant burden in terms of patients' quality of life (QoL) and work performance. It also represents a risk factor for other respiratory comorbidities in adults, especially asthma, and a precursor to learning disabilities, behavioural abnormalities, and psychological impairment in children.[10] Respiratory comorbidities are common in these patients due to the shared immunological pathogenesis as well as to the physical and biological link between upper and lower airways, synthesized in the concept on United Airway Disease, as discussed below.[11]

Sleep disturbances are frequent in both children and adults. Nasal congestion is the most common and bothersome symptom of rhinitis and is considered a major cause of sleep impairment in affected individuals. Sleep disturbance severity is directly related to the severity of the disease.[12,13]

Nasal obstruction commonly causes micro-arousals and sleep fragmentation and does act as an independent risk factor for obstructive sleep apnoea. Rhinitis alone is associated with mild obstructive sleep apnoea.[14] A systematic review including articles published over the past 25 years highlighted a statistically significant association between allergic rhinitis in children and sleep-disordered breathing, including snoring and obstructive sleep apnoea.[15] Along with the role of sleep apnoea as a risk factor for metabolic and cardiovascular diseases, sleep disturbances also represent a major determinant of impaired QoL in patients affected with rhinitis.[10,16]

Depression can also be considered a relevant and emerging allergic rhinitis comorbidity. According to a recent survey including 14 studies and overall 19.36±1.1 million participants, an association between allergic rhinitis and depression could be described, with 1.54 OR (95% CI 1.24 to 1.90, $p < 0.05$).[17] Along with psychological impairment, related to the impact of AR on QoL, other mechanisms might contribute to depression in allergic patients, in particular psychopathologies may be in part a consequence of neuro-inflammation due to the systemic spread of inflammatory cytokines in these patients.[17,18]

In addition, looking at the issue from another perspective, the complexity of the disease with its associated comorbidities implies a relevant economic burden of AR. Costs due to allergic rhinitis can be divided into two categories. The first consists of direct costs that are related to economic resources spent on disease management, including allergen avoidance, proper pharmacologic therapies, and allergen immunotherapy.[1,10] The second includes indirect and "hidden" costs that are due to missing work days and decreased productivity as far as costs associated with management of AR comorbidities, such as sinusitis and asthma.[19]

Prevalence of Allergic Rhinitis in Asthmatic Children

Allergic rhinitis is common in paediatric age worldwide, its prevalence ranging from 0.8% to 14.9% in 6–7-years old and 1.4% to 39.7% in 13–14-year-old children.[19] According to the ISAAC Phase III study, AR prevalence increased from 8.5% in children aged 6–7 years to 14.6% in those aged 13–14 years, especially in many low-income and middle-income countries (LMICs) whereas little change was observed in western Europe.[20] In 80% of cases, AR symptoms occur before the age of 20 years, and 40% of these cases developed symptoms before the age of 6 years.[21]

AR is frequently associated with other atopic diseases, including asthma, allergic conjunctivitis, and eczema. In particular, most patients with asthma have comorbid AR, whereas less than one-third of those with AR have asthma.[22] Indeed, epidemiological evidence indicates that about 30% of patients with rhinitis develop asthma during their life course[23] and up to 80% of persistent asthma subjects suffer from coexisting rhinitis.[24] Of note, the relationship between the over mentioned conditions has been relatively consistent over the years, despite changes in global prevalence.[25]

Overall, AR incidence in individuals with asthma appears to increase with age. Indeed, recent data have shown that adolescents with asthma have significantly more frequent comorbid rhinitis ($p = 0.02$; OR = 2.07) when compared with younger children.[26] In line with this finding, extensive prospective follow-up data from the MAS birth cohort study previously found that, at age 20, asthma occurred more frequently in association with AR than as a single entity.[27] When taking into account the patient's sensitization profile, despite previously published evidence of a more frequent association between allergic rather than non-allergic rhinitis and asthma,[28] more recently, the *Mechanisms of the Development of*

ALLergy (MeDALL) study, which included data from 12 European birth cohorts, showed that the coexistence of rhinitis and asthma is more common than expected by chance, regardless of IgE sensitization, suggesting that these diseases share causal mechanisms other than atopic sensitization.[29]

There is evidence that AR has an impact on asthma, as shown in a large school-based cohort study reporting that the majority of children had comorbid AR, which was associated with increased asthma morbidity. In particular, in comparison with children without AR, those with comorbid asthma and AR had significantly fewer symptom-free days ($p < 0.001$), more daytime symptoms ($p < 0.001$), more rescue medication use ($p < 0.01$), and more activity limitation due to asthma ($p < 0.001$).[30]

Taken together, these findings suggest that AR should be routinely investigated in children and adolescents with asthma in order to optimize treatment and achieve better asthma control and, likewise, the resolution of AR symptoms.

United Airways Disease: The Impact of Rhinitis on Asthma Control

The "United airways disease" (UAD) concept clearly defines that upper and lower airways are part of a single organ. Upper and lower airway diseases frequently co-occur, reflecting the existence of a common underlying immunological background. UAD includes rhinitis, chronic rhinosinusitis (CSR), nasal polyposis (NP), and concomitant/comorbid lower airways disorders: asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis (CF), and obstructive sleep apnoea (OSA).[11]

Under the epidemiological perspective, the cross-relationship between allergic rhinitis and asthma is clear-cut. As mentioned above, approximately 80% of asthma patients suffer from rhinitis, and 30% of patients with rhinitis have asthma. AR represents a significant risk factor for asthma (odds ratio, OR 3.5). The risk of asthma in AR is more evident in children than in adults (OR 4.1 vs 3.4).[31,32] The involvement of both upper and lower airways leads to a greater burden in terms of patients' health status and requires a more complex diagnostic and therapeutic plan.[11] Of note, even in the absence of symptomatic asthma, a relevant proportion of patients affected by AR do present airway hyper-responsiveness (AHR) documented by positive bronchial provocation test and reversible airflow obstruction. Non-asthmatic patients with AR also showed the presence of lower airway inflammation and some degree of airway remodeling.[33,34]

Different mechanisms may underlie the increased bronchial hyper-reactivity in the presence of an impaired nasal function. The loss of nasal function due to mucosal congestion and retention in the nasal cavity hampers the airflow through the upper airways in favour of oral respiration and oral breathing, which are associated with a higher risk of bronchospasm.[35] In fact, oral breathing bypasses the functional role of the nose in terms of warming and humidifying air, which therefore reaches the bronchi being cooler and drier. In addition, nasal mucus and mucus-ciliary apparatus filter the particles and gaseous materials in inhaled air before they reach the lower airways; on a functional ground, in the nose both innate and specific immune system cooperate to avoid infectious agent to reach the lower airways.[36,37] Therefore, nasal obstruction is strictly related to the allergens or cold air loading directly into the bronchial airways, and to the consequent increase of airways causing hyper-responsiveness.

Another mechanism that could underlie bronchial hyper-reactivity in AR patients is the so-called nasobronchial reflex. It represents a branch of the diving reflex, which physiologically leads to suppression of respiration, laryngospasm, and bronchoconstriction when the head is underwater water.[36] In that case, vagal and trigeminal pathways and afferent receptor site mediate broncho-constriction. However, the relevance of that mechanism in AR patients' bronchial hyper-responsiveness is still controversial.[37]

Finally, the increased reactivity of lower airways associated with AR could be explained in the wider perspective of T2 inflammation. In fact, it is well known that when performing nasal allergen provocation test, an allergic inflammatory response, characterised by increased eosinophils number in the nasal mucosa as well as in the peripheral blood can be observed in patients with AR. Eosinophils can selectively infiltrate different tissues, including bronchial wall. There they can impair the epithelial integrity, leading to a decrease in ciliated and brush cells, mast cell secretion, and the exposure of underlying sensory nerve endings, which finally promote bronchial hyper-responsiveness and bronchoconstriction.[38–40] Sedgwick et al authored an old but still pivotal study showing in the broncho-alveolar lavage fluid obtained from AR patients a significant increase in histamine and tryptase 12 minutes after challenge with antigen, and a further increase in

IL-5 concentrations that correlated with the presence of eosinophils and eosinophil granular proteins 48 hours after challenge. Neither eosinophils nor soluble mediators of eosinophils were increased in healthy control subjects.[41]

When considering the mechanisms discussed so far, the relevance of AR in asthma onset and control does not surprise. The presence of AR is a significant early-life predictor for an accelerated decline in lung function from the first to the sixth decade of life.[42] In particular, patients affected with AR not only are more prone to develop bronchial hyperresponsiveness and asthma compared with patients not suffering from AR, but suboptimal control of AR implies also a worse asthma control in those patients.[43] A growing evidence indicates that poor asthma control and higher medical resources use, including acute asthma exacerbations, emergency department visits, unscheduled and scheduled physician office visits, and prescription medication is more common in patients with a concomitant allergic rhinitis compared with those without allergic rhinitis.[13,43–45]

Diagnostic Work-Up and Differential Diagnosis

The clinical suspect of AR firstly relies on symptoms, including one or more of the following symptoms, such as pruritus, sneezing, rhinorrhoea, nasal congestion, and hyposmia that arise within minutes after the exposition to allergen until 1–2 hours; late symptoms are nasal obstruction, hyposmia, nasal hyper reactivity and post nasal mucous discharge.[46–48] Allergic rhinitis can be perennial or seasonal, according to the relevant allergen, but this classification is not applicable globally, so the Allergic Rhinitis and its Impact on Asthma (ARIA) group has classified AR into intermittent or persistent on the duration of symptoms.[22] The clinical history is essential for diagnosing and profiling rhinitis in children in order to provide the most appropriate treatment and to establish the best management for the patient.[49,50] The clinical history should point out where and when the nasal symptoms occur, the relieving or exacerbating factors such as environmental exposures to chemicals or tobacco at home or school or medications, and identify any trigger like pollen, house mould, trees, grass, dust mite, pets.[51] Comorbidities should also be assessed through the detection of their clinical manifestations such as coughing, wheezing, and shortness of breath suggest asthma; red, watery eyes, and hyperaemic conjunctiva suggest conjunctivitis; tiredness, snoring, sleep apnoea could be indicative of a sleep disorder; poor school performance, speech and learn disorder, poor concentration, high TV volume could be indirect signs suggestive of hearing difficulties due to chronic rhinosinusitis, otitis media with effusion, or adenoidal hypertrophy; other comorbidities to rule out are eczema, and pollen-food syndrome.[51] The clinical history assessment should include an investigation of the impact of rhinitis on daily life, school performance, and sleep, and detailed family history of allergic or immunological diseases.[50,51]

The examination should also include anthropometric measures and the evaluation of the skin, ear, nose, oral cavity, neck, and chest.[52,53] A general assessment is even more relevant in children in therapy with ongoing or long-term steroid treatment, in light of the well-known drug-related adverse events.[52] The typical signs of atopy are Dennie-Morgan lines, nasal crease, allergic salute, conjunctivitis, and allergic shiners.[54] Nasal inspection is provides an essential overview and it could be performed through anterior rhinoscopy or at least by an otoscope; secretions (usually watery in AR and discoloured in NAR or infectious rhinitis), crusts, foreign bodies, deviation of the septum, perforation of the septum, polyps, oedema of the mucosa can be typically observed. Nasal endoscopy is not mandatory but it should be considered especially in the case of perennial symptoms in order to exclude anatomical abnormalities or inflammatory conditions other than allergy (ie, chronic rhinosinusitis with or without nasal polyps); furthermore, it allows also to assess the nasal ostium patency, the adenoids size, or the presence of nasal tumors.[50,55] On a functional ground, nasal airflow should be tested, in order to detect unilateral or bilateral obstruction.

Defining the allergic sensitization profile through skin prick testing (SPT) or specific serum IgE,[46] is essential in light of a complete diagnostic work-up and for further treatment selection, especially if allergen immunotherapy (AIT) might be considered. SPT is the main in vivo test recommended by international guidelines, regarded as the most sensitive and specific test for atopy identification.[56] Of note, positive SPT alone does not confirm the AR diagnosisin fact, the detected sensitization must be consistent with the patient's clinical history in order to sustain a cause-effect relationship. The measurement of serum-specific IgE represents an in vitro test to explore the sensitization profile. From the methodological point of view, ImmunoCAP system (Thermo Fisher Scientific, TFS, Uppsala) allows a single allergen evaluation, whilst the Immuno-Solid Phase Allergen Chip (ImmunoCAP ISAC from TFS), and the Allergy Explorer-ALEX system

(Macroarray DX Wien, Austria) evaluate several allergens at the same time. All the mentioned tests have high sensibility and specificity, regardless of age and medication,[56] providing the opportunity to confirm AR diagnosis even during the course of antihistaminic treatment, which on the opposite hampers the skin reactivity and the reliability of SPT. Specific IgE detection is also helpful in differentiating cross-sensitization and to guide AIT extract selection.

In the upcoming future, other biomarkers could support the diagnosis of AR, such as circulating miRNA and metabolites.[57,58]

In the light of a personalized approach in terms of pharmacological treatment, and proper follow-up in the medium-long term, a careful differential diagnosis work up should be provided. In the case of discrepancy between sensitization profile and symptoms distribution across the year, or in patients presenting "atypical" clinical manifestation, a detailed investigation in terms of differential diagnosis is highly recommended.

For instance, imaging is not mandatory but in the suspect of sinusitis, a CT scan of nasal sinuses is indicated. In the differential diagnosis, AR must be distinguished from infectious rhinitis, usually secondary to viral infections, and from non-allergic and non-infectious rhinitis (NAR), which includes other disorders potentially presenting with rhinitis, such as those associated with exposure to irritants such as tobacco smoke, gastroesophageal reflux, and in older children hormonal dysfunction (hypothyroidism), specific medications, and vasomotor and idiopathic rhinitis.[53] Other differential diagnoses include local allergic rhinitis (LAR), mixed rhinitis, structural abnormalities, adenoidal hypertrophy, and other conditions that could mimic chronic rhinitis in paediatric patients, like primary immunodeficiency (PID), cystic fibrosis (CF), and primary chronic rhinosinusitis due to PID, CF, or primary ciliary dyskinesia (PCD).

On a clinical ground, AR might share the same symptoms with other conditions, misleading the diagnostic work-up. An alternative diagnosis should be considered in the presence of unilateral symptoms, isolated nasal obstruction, mucopurulent rhinorrhoea, posterior-rhinorrhoea with thick mucus and/or without anterior rhinorrhoea, pain, epistaxis, and anosmia.[22] For instance, a chronic mucopurulent discharge suggests infective rhinosinusitis secondary to adenoidal hypertrophy, anatomical abnormalities, PID, PCD, or CF.[53]

LAR is a rhinitis phenotype characterized by nasal T2 allergic inflammatory response with local production of specific IgE without evidence of atopy shown with SPT or serum-specific IgE. Most likely, LAR represents a subgroup previously defined as non-allergic rhinitis with eosinophilia syndrome (NARES).[59] That condition in children is highly under-diagnosed; the patients present symptoms and nasal hyper-reactivity and show a positive response to nasal provocation tests to aeroallergens.[60] Nasal challenge test, according to EAACI recommendations, can be performed above 5 years of life. The measurement of local IgE in the nasal lavage fluid provides a way to differentiate in the paediatric population LAR from NAR and to predict the response to the classic AR therapy.[61]

The basophil activation test could be used to support the diagnosis of LAR with high specificity,[57] but it is available only as a research tool.

NAR is considered more prevalent in adults but it is poorly defined in the paediatric population.[62] NAR is characterized by the presence of rhinitis, without systemic signs of allergic inflammation nor clinical signs of infection.[59] The term NAR, moreover, includes different types of rhinitis that were recently classified according to the European Academy of Allergy and Clinical Immunology (EAACI) as follows: drug-induced rhinitis, rhinitis of the elderly, hormonal rhinitis including pregnancy-induced rhinitis, non-allergic occupational rhinitis, gustatory rhinitis, and idiopathic rhinitis. Apart from a detailed medical history, it is important to perform an anterior rhinoscopy in order to exclude signs of infection, such as crusts, or anatomic anomalies.[59] Nasal endoscopy is also recommended by EAACI, to detect chronic rhinosinusitis with nasal polyps (CRSwNP) or chronic rhinosinusitis without nasal polyps (CRSsNP). EAACI does not recommend performing allergen provocation testing, microbiological analysis of the nasal content, and nasal cytology, that anyway may help to distinguish between an inflammatory or neurogenic aetiology of symptoms. In nasal cytology, eosinophilic inflammation could be detected and, in the absence of systemic allergy, may be attributed to LAR, NARES or to intolerance to drugs, aspirin, food or preservatives.

Pharmacological Treatment Options

The pharmacological treatment of AR in children in the last years has not substantially changed; on the other side, some improper options still represent common self-medication strategies. The currently available options can be used alone or

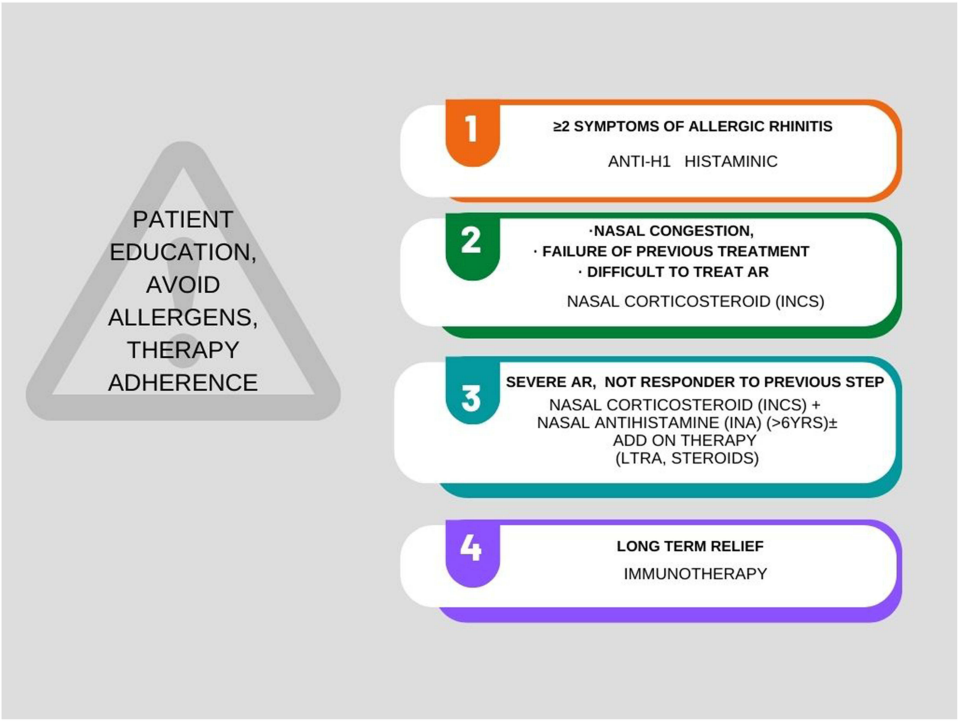

Figure 1 Overview of allergic rhinitis management.

in combination. Several international consensus have standardized and recommended an approach based on severity, chronicity, and response to treatment. Patients with mild intermittent symptoms for a short period benefit from short intermittent therapy, however patients with bothersome symptoms persisting for a long time do require regular treatment.

Education and allergen avoidance represent the first-line approach as they substantially help to control the allergen exposure; however, most patients require a stepwise approach to control symptoms, maintain a quality of life and avoid adverse events.[63] Both the EUFOREA algorithm and the American Academy of Allergy Asthma and Immunology suggest to base the management of paediatric AR on a stepwise pattern,[50,64] as summarized in Figures 1 and 2.

Oral Antihistamines

In clinical practice, oral antihistamines have been used for approximately 50 years as the first-line treatment for AR. However, controlled trials about the treatment for AR in children are substantially lacking.[50] Oral antihistamines that target H1 and H2 receptors are commonly available on the market and can be divided into old and new generation antihistamines, mainly differing by their ability to cross the blood brain barrier (BBB). The H1-antihistamines are highly lipophilic and cross the BBB potentially causing sedation. Furthermore, they act on peripheral inhibition of cholinergic, adrenergic, and muscarinic receptors. Especially in children, H1-antihistamines are not recommended in the light of their side effects including sleep cycle impairment, and increase the latency towards restful sleep, which correlates with poor school performance and bad or low grades in examination.[64] Second-generation H1 antagonists (loratadine, cetirizine, terfenadine and astemizole) are characterized by equivalent efficacy and safety in paediatric AR.[65] The main features of that class are reported in Table 1. Most second-generation antihistamines have good efficacy and a safety profile.

Oral antihistamines are recommended as first-line treatment in children with mild to moderate seasonal and mild perennial AR. A maintenance treatment is recommended during allergen exposure. In refractory patients (after 2–4 weeks of treatment) a step-up approach with intranasal corticosteroids (INCS) alone or in association with oral antihistamines should be considered.

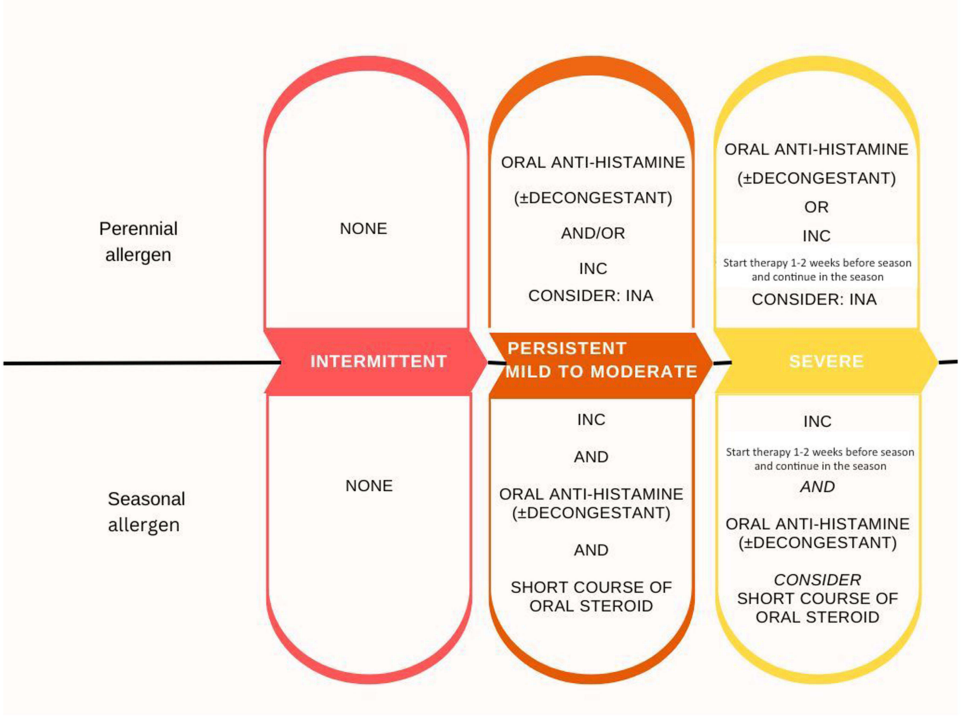

Figure 2 General approach to allergic rhinitis by symptoms severity and recurrence.

Intranasal Corticosteroids (INCS) with or without Intranasal Antihistamines (INA)

As discussed above, inflammatory cells and mediators in the nasal mucosa after allergen exposure drive the immunological background of AR. Two phases can be recognized within that inflammation cascade: the first one characterised by itching, rhinorrhoea and nasal pruritus, and the second one by nasal congestion.

Topical nasal corticosteroids (INCS) directly act on both the phases of the inflammatory response.[63–66] From the pharmacological perspective, it takes a few hours for the drug to become effective, although the clinical improvement could be seen after a few days or weeks, in particular the vasoconstriction effect. INCS act on the recruitment of inflammatory cells reducing epithelial cell activity, vascular permeability, and chemokine recruitment. INCS present an

Table 1 Characteristics of Second-Generation Oral Antihistamines

Drugs	Recommended Age	Pediatric Dose	Onset of Action (Hours)	Sedative Effect	Food Drug Interaction
Bilastine	≥6 yrs	10 mg (6–11 yrs) syrup or tablet 20 mg (>12 yrs)	<1	No	Yes
Cetirizina	≥2 yrs	2.5–5 mg (2–5 yrs) 5–10 mg od (6–11 yrs) syrup or tablet	0.7	Minimal	Yes
Desloratadine	≥6 months	1.25 mg (1–5 yrs) 2.5 mg (6–11 yrs)	1	No	No
Fexofenadine	≥2 yrs	30 mg tablet bid	2	No	Yes
Levocetirizine	≥6 months	5 mg (>6 yrs) od 1.25 mg (2–6 yrs) bid	1	No	No
Loratadine	≥2 yrs	10 mg via syrup or tablet	1	No	Yes

optimal safety profile to the high affinity to the receptor in nasal cells, and a negligible systemic effect.[67] The characteristics of most frequently used INCS are reported in Table 2.

Allergic rhinitis often represents a comorbidity in asthma children treated with inhaled corticosteroids and it is important to take into consideration the development of systemic side effects. In particular, in these patients, the growth reduction after the first years of therapy persists as lowered adult height. However, the benefit of these treatments on symptoms and prevention of disease evolution must be balanced with side effects and it is appropriate to use the lowest effective dose for symptoms control.[68] The use of INA allows to directly interfere with the local inflammation without any systemic adverse event and rare mild local side effects.

INCS alone can be used for all categories of AR while INCS in combination with INA is recommended in patients who do not respond to INCS mono-therapy.[68] The association of INCS-INA has been demonstrated to be superior to INCS alone because of the synergic effect of INA on INCS.[69] The treatment with INCS is indicated in mild perennial AR or moderate-to-severe AR for both seasonal and perennial allergy. The combination INCS-INA is recommended for moderate-to-severe AR and for patients presenting lower airways hyper-reactivity or recurrent complications.[50,59]

The choice between INA or INCS-INA is based on the combined evaluation of different factors such as patient compliance, symptom control, type of administration, age, adverse effect, nasal mucosa condition. If symptoms persist after the treatment, the patient should refer to a specialist for further diagnostic work-up.

It has been demonstrated the INCS superiority on oral antihistamines in treating nasal symptoms including rhinorrhoea, itch, obstruction, and post-nasal drip and in the case of coexisting allergic conjunctivitis and asthma.[70] INCS therapy might cause local adverse effects such as crusting, burning, epistaxis, nasal dryness, throat irritation, sneezing. The association of INCS-INA is associated with dryness and bitter taste. It is also important to prescribe INCS in children on the minimum age and dose recommendation as reported in Table 2. INCS should be avoided in patients with glaucoma. The correct technique to administer intranasal spray and the therapeutic adherence are essential to achieve the benefit from this treatment.[50,59]

Topical and Oral Decongestants

Decongestants act on α-adrenergic receptors causing vasoconstriction of the blood vessels and reduction of edema in the nasal mucosa, paranasal sinus and on upper airways. They can be administered topical or orally and have a rapid onset of action. Oral decongestants have more adverse effects compared to topical ones. The use for more than 10 days is contraindicated because it can cause medication-induced rhinitis. Oral decongestants are contraindicated in young children[71] and, generally speaking, are not recommended as a reference treatment, in consideration of the high incidence of adverse events as well as the lack of a specific action on the inflammatory background of AR. In selected cases, when the nose is completely obstructed a brief course is recommended, under specialist control.

Table 2 Characteristics of Intranasal Corticosteroids (INCS)

Drugs	Recommended Age	Pediatric Dose	Onset of Action	Effect on Growth
Beclometasone	≥6 yrs	1–2 puffs bid	Few days	Yes
Budesonide	≥6 yrs	1–2 puffs bid	Within 10 hours	Yes
Fluticasone furoato	≥2 yrs	1–2 puffs bid	Within 8 hour	NP
Fluticasone propionato	≥4 yrs	1–2 puffs bid	Within 12 hour	NP
Mometasone	≥2 yrs	1 puff od	Within 12 hour	No
Triamcinolone	≥2 yrs	2 puffs od/bid	Few days	NP

Leukotriene Receptor Antagonists

Leukotrienes have a relevant role in the pathogenesis of AR inducing inflammation, nasal congestion and obstruction and leukotriene receptor antagonist (LTRA) might be considered a kind of targeted therapy in AR. Montelukast is the most studied LTRA in rhinitis and it is indicated in the moderate-to-severe disease stages in both primary and secondary setting.[72] LTRAs are effective on nasal obstruction and as an add-on therapy to INCS and oral antihistamine, particularly for AR patients with bronchial asthma and suffering from night-time nasal symptoms.[50,72] Clinical response should be evaluated after 2 weeks of treatment in order to decide whether to maintain, step-up or step-down the therapy. LTRAs are also indicated as a second-line treatment in patients with AR and asthma not optimally controlled while using INCS. LTRAs can be prescribed as an additional therapy to the INCS + oral antihistamine combination in case of non-response. It may also be considered for RA with nocturnal symptoms and severe nasal blockage.[64] It is important to highlight that FDA warned about neuropsychiatric adverse events induced by montelukast and specified its use only for patients with AR refractory to other treatments.

Systemic Corticosteroids

The use of systemic corticosteroids in clinical practice has gradually reduced due to adverse events associated with their prolonged intake. In AR, they reduce eosinophil mediators in nasal secretion during late phase of AR inflammation but are not indicated as a standard treatment for AR. The indication for systemic steroids in secondary-care settings is restricted to very severe and therapy-resistant symptoms in patients with other comorbidities such as poorly or difficult to control asthma or nasal polyposis. Anyway, it is no longer considered as a maintenance therapy and, when required, a course of oral prednisone should not exceed 5 days.[50,65]

Immunotherapy and Its Preventive Effect on Disease Evolution

Allergen immunotherapy (AIT) is the only available disease-modifying option for allergic diseases; in fact, it is able to induce a permanent immunological tolerance in sensitised patients. Nevertheless, it is still underused, especially in the case of coexisting asthma. It usually includes a build up phase, consisting in the administration of progressively higher doses of the allergen extract, followed by a maintenance phase with a stable dose. AIT re-modulates the way the immune system reacts to allergens by shifting the inflammation response from T2 predominant to T1 predominant cascade. Production of allergen-specific IgG4, T regulatory cells and inhibition of specific IgE have been described as the key immunological effects of allergen immunotherapy.[73–75] Two main routes are currently practiced for AIT administration: subcutaneous (SCIT) and sublingual (SLIT). Both have similar efficacy in AR with a safety profile that favours SLIT.[76–79] Adverse drug reactions (ADR) are rare and in most cases related to local reactions (itching and swelling at site of injection or oral cavity), even if systemic reactions can rarely occur, mostly during the build-up phase.[76–79] SLIT is usually the preferred option for children, given the non-invasive and more tolerable route of administration.[80]

In AR, with/without conjunctivitis, AIT is indicated in patients with allergen sensitization confirmed by SPT or IgE, especially when symptom control cannot be obtained with first-line therapy.[81] Currently, registered products are approved for children older than 5 years old, but few studies explored AIT benefits in younger patients too, although adherence is a main issue in pre-scholar children.[82,83]

Contraindications to AIT include uncontrolled asthma, eosinophilic esophagitis and history of severe systemic or large local reactions to immunotherapy. Furthermore, some conditions potentially associated with a worst survival after an anaphylactic event or with reduced responsiveness to its treatment (ie, severe lung or heart disease, beta-blocker use, etc.) are considered relative contraindications, even if more relevant to adult population.[81]

The efficacy and safety of AIT in patients with AR have been demonstrated by many trials, demonstrating symptoms and QOL improvement, reduction in medication use and health-care costs as well as documenting a preventive effect on disease evolution from AR to asthma.[81,84,85] Real-world evidence recently confirmed such findings, and data on long-term effectiveness of AIT in AR and asthmatic patients are also available.[86–88]

The optimal AIT duration is still matter of debate: however, the currently available evidence sustains a 3 years term treatment as the minimal requirement for consolidating the long-term effect for years after therapy discontinuation.[89]

Another debated issue is related to the ideal timing of AIT initiation in the life-course: in the light of its disease modifying effect it is reasonable to start the treatment as early as possible, although some caution is recommended in children <4 years of age.[82]

As mentioned above, the early introduction of AIT has the chance to exert a preventive effect on asthma development particularly in children and adolescents with AR and grass/birch pollen allergy; in addition AIT reduces the risk of new allergen sensitization in such patients, though evidence on that is still weak.[90]

Besides its preventive effect, immunotherapy is effective as a treatment in allergic asthma patients. Trials showed better symptom control, reduced risk of exacerbations, greater chances of stepping down inhaled therapy and improvement in pulmonary function tests in asthma patients treated with HDM and pollen AIT.[91] The same data have been supported by recently published real-world evidence.[86,88] Following those results, current GINA (Global Initiative for Asthma) international recommendations advice to consider house dust mites AIT as complementary therapy in the early stage of asthma (step 1 to 4).[92] Cost effectiveness evaluation also favours AIT as the reduction in exacerbation, hospitalization and overall medication use in the long-term outweighs the initial expense.[86]

Of note, despite AIT is part of a precision medicine approach, the preventive identification of best responders among patients matching the prescription criteria is not possible at the moment. Furthermore, physiological attenuation or remission of allergic manifestations has been observed with the growth. However, the AR burden and related-impairment, even for a limited life time frame, and the opportunity to interfere with the potential disease evolution deserve the maximal consideration when evaluating AIT option. More accurate and sustainable biomarkers/predictors of response, which are currently under investigation, will support a more personalized approach.[93]

Conclusions

Despite its symptoms being commonly mild to moderate, AR cannot be considered a trivial condition. First of all because of its epidemiological relevance, especially in paediatric population; second, for its potentially high impact on quality of life, quality of sleep and daily performance, which can be difficult to perceive but not less relevant in the middle-long term. In addition, when considering asthma children population, AR is probably the most important risk factor for asthma onset and the most impactful extra-bronchial determinant of asthma control. Still, AR is often self-managed or its symptoms not adequately valued by the young patients or their parents. Self-management commonly brings to use incorrect or not recommended treatment options, including "alternative medicine" remedies, or to take the therapy according to improper schedule. That kind of approach is at risk of amplifying the disease burden and of reducing the chance of complete remission.

According to the evidence mentioned above every Health-Care Professional taking care of paediatric patients should be educated to recognize AR manifestations and aware of their potential burden, so that an appropriate diagnostic assessment can be performed and a correct management is established. In fact, the pharmacological treatment, if not properly tailored, might itself contribute to the disease burden, in terms of poor tolerability profile, when talking about antihistamines, or middle-long term well-known adverse events when taking into consideration corticosteroids, whether systemic or even local.

Under this perspective, AIT should always be considered in the light of a precision medicine approach. In fact, AIT does represent a unique opportunity to specifically interfere with AR immunological background, to improve both AR and bronchial asthma control and to prevent allergic disease evolution. Although in the past bronchial asthma had been considered a relative or absolute contraindication, depending on its severity and control, the recent evidence in terms of both safety and efficacy profile paves the way for a new perspective to look at the issue. In other words, in AR patients with coexisting bronchial asthma, the last should be considered a further major indication for AIT. Of note, in the case of uncontrolled asthma, achieving an optimal disease control should be considered a priority before prescribing AIT. In addition, an increasing amount of evidence is going to support the potential of AIT in preventing AR evolution towards asthma development in affected children. Thus, verifying the patient's eligibility to that option should be considered as a priority for every physician managing children suffering from AR, whether or not associated with bronchial asthma.

Funding

There is no funding to report.

Disclosure

All the Authors declare no conflict of interest.

References

1. Liva GA, Karatzanis AD, Prokopakis EP. Review of rhinitis: classification, types, pathophysiology. *J Clin Med*. 2021;10(14):3183. doi:10.3390/jcm10143183
2. Papadopoulos NG, Guibas GV. *Rhinitis Subtypes, Endotypes, and Definitions. Vol. 36, Immunology and Allergy Clinics of North America*. W.B. Saunders; 2016:215–233.
3. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol*. 2001;108(1 Suppl):S2–8. doi:10.1067/mai.2001.115569
4. Marple BF. Allergic rhinitis and inflammatory airway disease: interactions within the unified airspace. *Am J Rhinol Allergy*. 2010;24:249–254. doi:10.2500/ajra.2010.24.3499
5. Bousquet J, Schünemann HJ, Togias A, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. *J Allergy Clin Immunol*. 2020;145(1):70–80.e3. doi:10.1016/j.jaci.2019.06.049
6. Sin B, Togias A. Pathophysiology of allergic and nonallergic rhinitis. In: Proceedings of the American Thoracic Society; 2011:106–114.
7. Bentley A, Jacobson M, Cumberworth V, et al. Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. *J Allergy Clin Immunol*. 1992;89(4):877–883. doi:10.1016/0091-6749(92)90444-7
8. Cingi C, Gevaert P, Mösges R, et al. Multi-morbidities of allergic rhinitis in adults: European Academy of Allergy and Clinical Immunology Task Force report. *Clin Transl Allergy*. 2017;7:17. doi:10.1186/s13601-017-0153-z
9. Pawankar R. The WAO white book on allergy. 2013.
10. Meltzer EO, Blaiss MS, Naclerio RM, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. *Allergy Asthma Proc*. 2012;33(Suppl 1):S113–41. doi:10.2500/aap.2012.33.3603
11. Tiotiu A, Novakova P, Baiardini I, et al. Manifesto on united airways diseases (UAD): an Interasma (global asthma association–GAA) document. *J Asthma*. 2022;59(4):639–654. doi:10.1080/02770903.2021.1879130
12. Craig TJ, Sherkat A, Safaee S. Congestion and sleep impairment in allergic rhinitis. *Curr Allergy Asthma Rep*. 2010;10(2):113–121. doi:10.1007/s11882-010-0091-5
13. Meltzer EO. Allergic rhinitis. Burden of illness, quality of life, comorbidities, and control. *Immunol Allergy Clin North Am*. 2016;36(2):235–248. doi:10.1016/j.iac.2015.12.002
14. Staevska MT, Mandajieva MA, Dimitrov VD. Rhinitis and sleep apnea. *Curr Allergy Asthma Rep*. 2004;4(3):193–199. doi:10.1007/s11882-004-0026-0
15. Lin SY, Melvin TAN, Boss EF, Ishman SL. The association between allergic rhinitis and sleep-disordered breathing in children: a systematic review. *Int Forum Allergy Rhinol*. 2013;3(6):504–509. doi:10.1002/alr.21123
16. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol*. 2009;124(3):S43–70. doi:10.1016/j.jaci.2009.05.013
17. Wang J, Xiao D, Chen H, Hu J. Cumulative evidence for association of rhinitis and depression. *Allergy Asthma Clin Immunol*. 2021;17(1):111. doi:10.1186/s13223-021-00615-5
18. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446–457. doi:10.1016/j.biopsych.2009.09.033
19. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8(3):483–491. doi:10.1183/09031936.95.08030483
20. Asher MI, Montefort S, Björkstén B, et al.; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733–743. doi:10.1016/S0140-6736(06)69283-0
21. Licari A, Ciprandi G, Marseglia A, et al. Current recommendations and emerging options for the treatment of allergic rhinitis. *Expert Rev Clin Immunol*. 2014;10(10):1337–1347. doi:10.1586/1744666X.2014.955476
22. Bousquet J, Khaltaev N, Cruz AA, et al.; World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8–160. doi:10.1111/j.1398-9995.2007.01620.x
23. Cruz AA, Popov T, Pawankar R, et al.; ARIA Initiative Scientific Committee. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy*. 2007;62(Suppl 84):1–41. doi:10.1111/j.1398-9995.2007.01551.x
24. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126:466–476. doi:10.1016/j.jaci.2010.06.047
25. Asher MI, Stewart AW, Wong G, et al.; ISAAC Phase Three Study Group. Changes over time in the relationship between symptoms of asthma, rhinoconjunctivitis and eczema: a global perspective from the International Study of Asthma and Allergies in Childhood (ISAAC). *Allergol Immunopathol*. 2012;40(5):267–274. doi:10.1016/j.aller.2011.11.004
26. Tosca MA, Pistorio A, Silvestri M, et al; "ControL'Asma" Study Group. The comparison between children and adolescents with asthma provided by the real-world "ControL'Asma" study. *J Asthma*. 2022;59(8):1531–1536. doi:10.1080/02770903.2021.1941089
27. 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;26:431–437. doi:10.1111/pai.12410
28. Cibella F, Cuttitta G, La Grutta S, et al. Proportional Venn diagram and determinants of allergic respiratory diseases in Italian adolescents. *Pediatr Allergy Immunol*. 2011;22(1 Pt 1):60–68. doi:10.1111/j.1399-3038.2010.01097.x
29. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. *Lancet Respir Med*. 2014;2(2):131–140. doi:10.1016/S2213-2600(13)70277-7

30. Stern J, Chen M, Fagnano M, et al. Allergic rhinitis comorbidity on asthma outcomes in city school children. *J Asthma*. 2022;1–7. doi:10.1080/02770903.2022.2043363
31. Tiotiu A, Plavec D, Novakova S, et al. Current opinions for the management of asthma associated with ear, nose and throat comorbidities. *Eur Respir Rev*. 2018;27(150):180056. doi:10.1183/16000617.0056-2018
32. Tohidinik HR, Mallah N, Takkouche B. History of allergic rhinitis and risk of asthma; a systematic review and meta-analysis. *World Allergy Organ J*. 2019;12(10):100069. doi:10.1016/j.waojou.2019.100069
33. Iyer A, Athavale A. Nasal airway resistance and latent lower airway involvement in allergic rhinitis. *J Assoc Physicians India*. 2020;68(3):43–47.
34. Chakir J, Laviolette M, Boutet M, Laliberté R, Dubé J, Boulet LP. Lower airways remodeling in nonasthmatic subjects with allergic rhinitis. *Lab Invest*. 1996;75(5):735–744.
35. Shturman-Ellstein R, Zeballos RJ, Buckley JM, Souhrada JF. The beneficial effect of nasal breathing on exercise-induced bronchoconstriction. *Am Rev Respir Dis*. 1978;118(1):65–73. doi:10.1164/arrd.1978.118.1.65
36. van Cauwenberge P, Sys L, de Belder T, Watelet JB. Anatomy and physiology of the nose and the paranasal sinuses. *Immunol Allergy Clin North Am*. 2004;24(1):1–17. doi:10.1016/S0889-8561(03)00107-3
37. Liu Y, Sha J, Meng C, Zhu D. Mechanism of lower airway hyperresponsiveness induced by allergic rhinitis. *J Immunol Res*. 2022;2022:1–8.
38. Frigas E, Gleich GJ. The eosinophil and the pathophysiology of asthma. *J Allergy Clin Immunol*. 1986;77(4):527–537. doi:10.1016/0091-6749(86)90341-6
39. Flavahan NA, Slifman NR, Gleich GJ, Vanhoutte PM. Human eosinophil major basic protein causes hyperreactivity of respiratory smooth muscle. Role of the epithelium. *Am Rev Respir Dis*. 1988;138(3):685–688. doi:10.1164/ajrccm/138.3.685
40. Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am Rev Respir Dis*. 1985;131(4):599–606. doi:10.1164/arrd.1985.131.4.599
41. Sedgwick JB, Calhoun WJ, Gleich GJ, et al. Immediate and late airway response of allergic rhinitis patients to segmental antigen challenge. Characterization of eosinophil and mast cell mediators. *Am Rev Respir Dis*. 1991;144(6):1274–1281. doi:10.1164/ajrccm/144.6.1274
42. Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med*. 2018;6(7):535–544. doi:10.1016/S2213-2600(18)30100-0
43. de Groot EP, Nijkamp A, Duiverman EJ, Brand PLP. Allergic rhinitis is associated with poor asthma control in children with asthma. *Thorax*. 2012;67(7):582–587. doi:10.1136/thoraxjnl-2011-201168
44. Belhassen M, Demoly P, Bloch-Morot E, et al. Costs of perennial allergic rhinitis and allergic asthma increase with severity and poor disease control. *Allergy*. 2017;72(6):948–958. doi:10.1111/all.13098
45. Gaugris S, Sazonov-Kocevar V, Thomas M. Burden of concomitant allergic rhinitis in adults with asthma. *J Asthma*. 2006;43(1):1–7. doi:10.1080/02770900500446823
46. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet*. 2011;378(9809):2112–2122. doi:10.1016/S0140-6736(11)60130-X
47. Kim JY, Lee S, Suh DI, et al. Distinct endotypes of pediatric rhinitis based on cluster analysis. *Allergy Asthma Immunol Res*. 2022;14(6):730–741. doi:10.4168/aair.2022.14.6.730
48. Shin SH, Ye MK, Park J, Geum S-Y. Immunopathologic role of eosinophils in eosinophilic chronic rhinosinusitis. *Int J Mol Sci*. 2022;23(21):13313. doi:10.3390/ijms232113313
49. Bousquet J, Sousa-Pinto B, Anto JM, et al. Identification by cluster analysis of patients with asthma and nasal symptoms using the MASK-air® mHealth app. *Pulmonology*. 2022;S2531-0437(22)00252–5. doi:10.1016/j.pulmoe.2022.10.005
50. Scadding GK, Smith PK, Blaiss M, et al. Allergic rhinitis in childhood and the new EUFOREA algorithm. *Front Allergy*. 2021;2:706589. doi:10.3389/falgy.2021.706589
51. Doulaptsi M, Aoi N, Kawauchi H, et al. Differentiating rhinitis in the paediatric population by giving focus on medical history and clinical examination. *Med Sci*. 2019;7(3):38–52.
52. Campbell RG. Risks and management of long-term corticosteroid use in chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg*. 2018;26(1):1–7. doi:10.1097/MOO.0000000000000421
53. Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2013;68(9):1102–1116. doi:10.1111/all.12235
54. Zhang B, Ma L. Transverse nasal creases. *N Engl J Med*. 2021;385(24):2281. doi:10.1056/NEJMicm2111716
55. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;29:1–464.
56. Testera-Montes A, Jurado R, Salas M, et al. Diagnostic tools in allergic rhinitis. *Front Allergy*. 2021;2:721851. doi:10.3389/falgy.2021.721851
57. Breiteneder H, Peng YQ, Agache I, et al. Biomarkers for diagnosis and prediction of therapy responses in allergic diseases and asthma. *Allergy*. 2020;75(12):3039–3068. doi:10.1111/all.14582
58. Mastrorilli C, Posa D, Cipriani F, Caffarelli C. Asthma and allergic rhinitis in childhood: what's new. *Pediatr Allergy Immunol*. 2016;27(8):795–803. doi:10.1111/pai.12681
59. Hellings PW, Klimek L, Cingi C, et al. Non-allergic rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2017;72:1657–1665. doi:10.1111/all.13200
60. Papadopoulos NG, Aggelides X, Stamataki S, et al. New concepts in pediatric rhinitis. *Pediatr Allergy Immunol*. 2021;32(4):635–646. doi:10.1111/pai.13454
61. Colavita L, Catalano N, Sposito G, et al. Local allergic rhinitis in pediatric patients: is IgE dosage in nasal lavage fluid a useful diagnostic method in children? *Int J Mol Cell Med*. 2017;6(3):174–182. doi:10.22088/acadpub.BUMS.6.3.174
62. Poddighe D, Gelardi M, Licari A, Del Giudice MM, Marseglia GL. Non-allergic rhinitis in children: epidemiological aspects, pathological features, diagnostic methodology and clinical management. *World J Methodol*. 2016;6(4):200–213. doi:10.5662/wjm.v6.i4.200
63. Schuler CF, Montejo JM. Allergic rhinitis in children and adolescents. *Immunol Allergy Clin North Am*. 2021;41(4):613–625. doi:10.1016/j.iac.2021.07.010
64. Schenkel EJ. Paediatric issues relating to the pharmacotherapy of allergic rhinitis. *Expert Opin Pharmacother*. 2000;1(7):1289–1306. doi:10.1517/14656566.1.7.1289
65. Abdullah B, Latiff AHA, Manuel AM, et al. Pharmacological management of allergic rhinitis: a consensus statement from the Malaysian Society of Allergy and Immunology. *J Asthma Allergy*. 2022;15:983–1003. doi:10.2147/JAA.S374346

66. Khattiyawittayakun L, Seresirikachorn K, Chitsuthipakorn W, Kanjanawasee D, Snidvongs K. Effects of double-dose intranasal corticosteroid for allergic rhinitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2019;9(1):72–78. doi:10.1002/alr.22204
67. Jang TY, Kim YH. Recent updates on the systemic and local safety of intranasal steroids. *Curr Drug Metab*. 2016;17(10):992–996. doi:10.2174/1389200218666161123123516
68. William Kelly H, Sternberg AL, Lescher R, et al.; CAMP Research Group. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012;367(10):904–912. doi:10.1056/NEJMoa1203229
69. Du K, Qing H, Zheng M, Wang X, Zhang L. Intranasal antihistamines is superior to oral H1 antihistamines as an add-on therapy to intranasal corticosteroids for treating allergic rhinitis. *Ann Allergy Asthma Immunol*. 2020;125(5):589–596.e3. doi:10.1016/j.anai.2020.06.038
70. Vervloet D, Charpin D, Desfougeres JL. Intranasal fluticasone once daily compared with once-daily cetirizine in the treatment of seasonal allergic rhinitis: results of a multicentre, double-blind study. *Clin Drug Investig*. 1997;13(6):291–298. doi:10.2165/00044011-199713060-00001
71. Deckx L, de Sutter AI, Guo L, et al. Nasal decongestants in monotherapy for the common cold. *Cochrane Database Syst Rev*. 2016;10:CD009612. doi:10.1002/14651858.CD009612.pub2
72. Krishnamoorthy M, Mohd Noor N, Mat Lazim N, et al. Efficacy of montelukast in allergic rhinitis treatment: a systematic review and meta-analysis. *Drugs*. 2020;80:1831–1851. doi:10.1007/s40265-020-01406-9
73. Gazi U, Bahceciler NN. Immune mechanisms induced by sublingual immunotherapy in allergic respiratory diseases. *Clin Exp Immunol*. 2022;2022:uxac075.
74. Zhang Y, Lan F, Zhang L. Update on pathomechanisms and treatments in allergic rhinitis. *Allergy*. 2022;77:3309–3319. doi:10.1111/all.15454
75. Djuric-Filipovic I, Caminati M, Filipovic D, Salvottini C, Zivkovic Z. Effects of specific allergen immunotherapy on biological markers and clinical parameters in asthmatic children: a controlled-real life study. *Clin Mol Allergy*. 2017;15(1):7. doi:10.1186/s12948-017-0064-5
76. Liu W, Zeng Q, He C, et al. Compliance, efficacy, and safety of subcutaneous and sublingual immunotherapy in children with allergic rhinitis. *Pediatr Allergy Immunol*. 2021;32:86–91. doi:10.1111/pai.13332
77. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveil- lance study of subcutaneous immunotherapy, years 2008–2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract*. 2014;2:161–167.e3. doi:10.1016/j.jaip.2014.01.004
78. Caminati M, Dama AR, Djuric I, et al. Incidence and risk factors for subcutaneous immunotherapy anaphylaxis: the optimization of safety. *Expert Rev Clin Immunol*. 2015;11(2):233–245. doi:10.1586/1744666X.2015.988143
79. Senna G, Caminati M, Canonica GW. Safety and tolerability of sublingual immunotherapy in clinical trials and real life. *Curr Opin Allergy Clin Immunol*. 2013;13(6):656–662. doi:10.1097/ACI.0000000000000007
80. Đurić-filipović I, Caminati M, Kostić G, Filipović Đ, Živković Z. Allergen specific sublingual immunotherapy in children with asthma and allergic rhinitis. *World J Pediatr*. 2016;12(3):283–290. doi:10.1007/s12519-016-0022-1
81. Roberts G, Pfaar O, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy*. 2018;73:765–798. doi:10.1111/all.13317
82. Panganiban CM, Tam JS. Considerations in allergen immunotherapy for allergic asthma in pediatric patients under 4 years of age. *Ann Allergy Asthma Immunol*. 2021;126:314–315. doi:10.1016/j.anai.2021.02.007
83. Pajno GB, Caminiti L, Crisafulli G, et al. Adherence to sublingual immunotherapy in preschool children. *Pediatr Allergy Immunol*. 2012;23:688–689. doi:10.1111/j.1399-3038.2012.01317.x
84. Dhami S, Nurmatov U, Arasi S, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. *Allergy*. 2017;72:1597–1631.
85. Meltzer EO, Wallace D, Friedman HS, et al. Meta-analyses of the efficacy of pharmacotherapies and sublingual allergy immunotherapy tablets for allergic rhinitis in adults and children. *Rhinology*. 2021. doi:10.4193/Rhin21.054
86. Fritzsching B, Contoli M, Porsbjerg C, et al. Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: results from the REACT study, a retrospective cohort study. *Lancet Reg Health Eur*. 2021;13. doi:10.1016/j.lanepe.2021.100275
87. Calderón MA, Bacharier LB. Controversies in allergy: a pro/con review of sublingual allergen immunotherapy and allergic asthma. *J Allergy Clin Immunol Pract*. 2021;9:1818–1825. doi:10.1016/j.jaip.2021.02.029
88. Zielen S, Devillier P, Heinrich J, et al. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy*. 2018;73:165–177. doi:10.1111/all.13213
89. 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;125:131–138.e7. doi:10.1016/j.jaci.2009.10.035
90. Halken S, Larenas-Linnemann D, Roberts G, et al. EAACI guidelines on allergen immunotherapy: prevention of allergy. *Pediatr Allergy Immunol*. 2017;28:728–745. doi:10.1111/pai.12807
91. Agache I, Lau S, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: house dust mite-driven allergic asthma. *Allergy*. 2019;74:855–873. doi:10.1111/all.13749
92. Global initiative for asthma. Available from: https://ginasthma.org/. Accessed December 28, 2022.
93. de Vos G, Viswanathan S, Pichardo Y, et al. A randomized trial of subcutaneous allergy immunotherapy in inner-city children with asthma less than 4 years of age. *Ann Allergy Asthma Immunol*. 2021;126:367–377.e5. doi:10.1016/j.anai.2020.12.016