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CURRENT OPINION

Pediatric Allergic Rhinitis and Asthma: Can the March be Halted?

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Abstract The strong epidemiologic and pathophysiologic link between allergic rhinitis (AR) and asthma has led to the concept of 'united airways disease' or 'respiratory allergy', implying that allergy, in its widest sense, underlies this clinical syndrome. Progression from AR to asthma is frequent and part of the 'atopic march'. Since pediatric immune responses are more adaptable and therefore may be more amenable to treatment, interventions at early childhood are characterized by a higher chance to affect the natural history of respiratory allergy. Although current treatments are quite effective in alleviating respiratory allergy symptoms, it has proven much more difficult to confirm any influence on the progression of the disease. Much more promising is the field of specific allergen immunotherapy, where current evidence, although not yet of ideal robustness, points towards a disease-modifying effect. In addition, newer or emerging, possibly more effective or more targeted interventions are promising in the preventive sense.

1 Introduction

The anatomic and functional relationship between upper (nasal cavities/paranasal sinuses) and lower (bronchi/bronchioles) airways has been the object of great interest in epidemiologic and pathophysiologic studies. Knowledge of respiratory diseases affecting both the nose and the lungs has helped us understand and regard these two parts of the respiratory system as a unique entity. These observations have been particularly studied in allergic respiratory diseases [1], i.e. allergic rhinitis (AR) and asthma, and terms proposed to represent this unity are: "one airway, one disease" [2], "allergic rhinobronchitis" [3], and "united airways disease" [4]. Taking into consideration differences between upper and lower airway physiology and pathology, another holistic approach comes under the term "chronic allergic respiratory syndrome" [5] or "respiratory allergy" [6], which implies that allergy in its broadest sense is the major underlying pathophysiology. Progression from AR to asthma can occur and is described as the "allergic" or "atopic march". Although AR usually precedes asthma (or appears simultaneously) [4, 7, 8], the opposite can be observed, often in preschoolers. In fact, in children, atopic dermatitis usually represents the first step of the atopic march, followed by allergic respiratory symptoms. The purpose of this article is to review the evidence supporting the link in pediatric respiratory allergy and discuss interventions that could prevent disease progression.

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2 Allergic Rhinitis and Asthma Link

Several factors support the respiratory allergy concept including common epidemiologic and pathophysiologic characteristics, genetic links, as well as treatment outcomes on both AR and asthma.

2.1 Epidemiologic Evidence

Wide variations in prevalence of pediatric AR and asthma have been reported in epidemiologic studies. Despite these

limitations, data from the current literature are indicative. Some of these are recorded in Table 1.

In adults and adolescents, cross-sectional epidemiological data have consistently shown that asthma and rhinitis often coexist [1]. In concordance is the pediatric input. Variation rates in ISAAC (International Study of Asthma and Allergies in Childhood), the largest pediatric multicenter cross-sectional study, were indeed striking (Table 1), but significant correlations ($r = 0.75$, $P < 0.0001$) between the prevalence of asthma and AR symptoms in the 13- to 14-year-olds were noted [9, 10]. Recently, Chawes et al. [13] reported on COPSAC (the Copenhagen Prospective Study on Asthma in Childhood), in which 13 % of the 7-year-olds had doctor-diagnosed (interview plus serum IgE) AR with an increased prevalence of asthma compared with the asymptomatic controls (21 vs. 5 %; $P < 0.002$). Analyzing data from the Arizona TCRS (Tucson Children's Respiratory Study) birth cohort, Wright et al. [14] noted that by the age of 6 years, 21 % of the children had AR (rhinitis plus ≥1 positive Skin Prick Test), and among the atopic children with physician-diagnosed AR the prevalence of asthma was 32 %. Retrospective studies also point towards the same data. During 1998–2001, a UK cohort study involving general practitioner medical records of 6- to 15-year-olds showed that 19.7 % of the asthmatic patients had AR [15]. Similarly, in the Norway National Database, 26.8 % of the children with at least one hospital admission for asthma, over a 2-year period, had a documented history of AR [16].

Longitudinal studies conducted in order to elucidate the natural history of these two respiratory allergic diseases revealed that AR usually precedes the onset of asthma. In children, available data assessing the temporal relationship between AR and asthma are less adequate. The population-based birth cohort BAMSE (Barn/Children, Allergy/Asthma, Milieu, Stockholm, Epidemiologic) study of children born during 1994–1996 in Stockholm, Sweden, revealed that 5.4 % of the 4-year-olds had AR, significantly associated with asthma (17.3 %, $P < 0.001$) at the age of 8 years [12]. In the TCRS [14], comparing children who developed rhinitis by the first year of life with those who developed it after, showed that by the age of 6 years it was more probable for them to be physician-diagnosed with AR (77 vs. 57 %, $P < 0.00005$) and twice as likely to develop asthma (23 vs. 13 %, $P < 0.005$). The association between childhood AR and asthma later in life was examined in the 37-year Tasmanian Asthma Study [17]. Childhood AR increased the likelihood of new-onset asthma in and after childhood 2- to 7-fold and the likelihood of having persisting asthma from childhood into middle-age 3-fold.

In fact, it has been suggested that allergic (or not) rhinitis might itself be an independent risk factor for asthma [1, 5]. However, although the link is well-established, a causal relationship is not and it is possible that AR and asthma are both manifestations of an underlying systemic allergic tendency [18]. In any case, the association between these two conditions renders children with AR to be mandatory assessed for asthma and vice versa [19, 20].

2.2 Pathophysiologic Evidence

The common AR and asthma immunopathology and immunopathophysiology has been shown in a number of studies and several mechanisms have been held responsible for this interaction: the respiratory (unprotected lower airways due to reduced filter and air-conditioning function of the nose), neural (nasobronchial reflex), and circulatory pathway [21]. The latter, concerning the systemic dissemination of inflammation, is considered the most relevant factor.

As both AR and asthma are inflammatory diseases with common triggers, they also have similar inflammatory mechanisms mediated by various cell types. Several mediators, the locally and systemically produced IgE and the systemic cross-talk with the bone marrow [22], all compose a common linking ground. This unifying concept has also been supported by studies involving allergen provocations: allergen-induced inflammatory infiltration

Table 1 Cross-sectional epidemiologic data on allergic rhinitis and asthma prevalence

Study	Year conducted	Number of subjects included	Age of subjects (in years)	AR (%)	Asthma (%)
ISAAC [9]	Mid 1990s	257,800	6–7	0.8–14.9	4.1–32.1
ISAAC [9]	Mid 1990s	463,801	13–14	1.4–39.7	2.1–32.2
SCARPOL [11]	1992	988	5–7	5	8.8
SCARPOL [11]	2001	1,274	5–7	4.6	7.4
BAMSE [12]	1998–2000	2,024	4	5.4	7.5
BAMSE [12]	2002–2004	2,024	8	14	7.3

AR allergic rhinitis, *BAMSE* Barn/Children, Allergy/Asthma, Milieu, Stockholm, Epidemiologic, *ISAAC* International Study of Asthma and Allergies in Childhood, *SCARPOL* Swiss Surveillance Programme on Childhood Allergy and Respiratory symptoms with respect to Air Pollution

and mediator's mobility doesn't differ between nasal and bronchial fluids or nasal and bronchial mucosa [5]. Braunstahl et al. [23] found a significant increase in nasal and bronchial epithelium eosinophils 24 h after nasal allergen provocation in non-asthmatics with seasonal AR, directly related to the expression of adhesion molecules. Blood eosinophils and interleukin (IL)-5 were also raised. This bidirectional cross-talk was evident when the same authors confirmed nasal inflammatory response after segmental bronchial allergen provocation in non-asthmatics with AR [24, 25]. Typical early- and late-phase responses are also essential common features between AR and asthma [5].

Some studies simultaneously performed in both the nose and the bronchi have shown that the extent of inflammation may vary [26]. Intrinsic differences between nasal and bronchial mucosa may be responsible for the less impressive evidence for tissue remodeling in AR [5]. Similarities and differences between the nasal and bronchial inflammatory mucosa are summarized in Table 2.

Non-asthmatic children with AR often have increased bronchial hyper-responsiveness (BHR) to methacholine, adenosine [27], or histamine, exercise or bronchial challenge [28], especially during and slightly after pollen season. Indeed, Cuttitta et al. [29] evaluated the prevalence of BHR in children with AR by methacholine bronchial challenge: non-asthmatics displayed a high prevalence of BHR, significantly associated with persistent AR. In concordance, a recent systematic review reporting on the influence of AR on exhaled nitric oxide (eNO) values, a non-invasive marker of lower airway inflammation, concluded that it was higher in children with AR than in children with non-AR, without rhinitis, or atopic children [30].

The above-mentioned studies demonstrate that AR is not just a local disease but that the entire respiratory tract is involved, even in the absence of clinical asthma [21].

2.3 Genetic Link

A number of genome-wide association studies have revealed that different allergic diseases share overlapping susceptibility loci. The C11orf30/LRRC32 region on chromosome 11q13.5 is associated with atopic dermatitis, asthma, and AR [31]. These overlapping loci could play an important role in the allergic march but further studies are needed to clarify the mechanisms underlying this phenomenon.

2.4 Therapeutic Link

Studies regarding therapeutic aspects of AR and asthma indicate that treatments targeting either of them may alleviate the coexisting condition [16, 32]. There are strong indications from observational data that treating co-morbid AR may result in better asthma outcomes in terms of asthma symptoms, emergency department visits and hospitalizations, and lower overall costs [33].

3 From Allergic Rhinitis to Asthma: Can it be Prevented?

Data indicating a link between AR and asthma and longitudinal studies on the association of childhood AR and asthma later in life are compelling. The hypothesis that AR might itself be an asthma risk factor is of particular interest and clinical implications are obvious; one could speculate that asthma burden in later life might be reduced by more focused treatment of AR in early life. Pediatric immune responses are more adaptable and therefore may be more amenable to treatment. Thus, early childhood offers a window of opportunity for interventions with a higher chance to affect the natural history of respiratory allergy [34]. Inevitably, the important question that rises is whether the current treatment choices available for AR could

Table 2 Similarities and differences between the nasal and bronchial inflammatory mucosa

	Nasal mucosa	Bronchial mucosa
Structural changes	Minimal epithelial damage	Extended epithelial damage
	No evidence of vascular remodeling	Proliferation of blood vessels
	Minimal collagen and fibrous deposition	Subepithelial fibrosis from deposition of collagen and proteoglycans under the basement membrane
	No smooth muscles	Airway smooth muscle hypertrophy and hyperplasia
Cytology		
Eosinophils	Increased	Increased
Neutrophils	Low numbers	Increased in severe asthma
T-cells	CD4+ increased	CD4+ increased
CD68	Possibly increased numbers	Often increased numbers

be characterized as disease modifying, capable of preventing the evolution of AR to asthma.

Management of AR in children tends to follow the same rationale as that in adults and includes avoidance of relevant allergens, pharmacotherapy, and specific immunotherapy.

3.1 Allergen Avoidance

Attempts to prevent exacerbations and treat AR by allergen avoidance have produced conflicting results. Outdoor allergens, such as pollen, cannot be completely avoided. Few studies have investigated the effectiveness of avoidance measures of indoor allergens on AR. On the whole the studies have been small and with methodologic challenges, making it difficult to offer any definitive recommendations on the role, if any, of house dust mite (HDM) avoidance measures in particular. The results of these studies have been assessed by a recent systematic review [35] concluding that interventions that achieve substantial reductions in HDM load may offer some benefit in reducing rhinitis symptoms. As far as cat dander prevention outcomes, a study on adults with asthma and/or AR indicated that the combination of a HEPA (high-efficiency particulate air) room air-cleaner, mattress and pillow covers, and bedroom cat exclusion did reduce airborne cat-allergen levels, but had no effect on disease activity for any parameter studied [36]. On the contrary, another small study found that cat-allergen load decrease had a significant effect on AR symptoms [37]. In conclusion, although the general consensus is that allergen avoidance should lead to symptom improvement, there is little evidence to support this through the use of physical or chemical methods and there is no evidence to support a possible secondary prevention effect on asthma development in AR subjects. Nevertheless, it is still conceivable that long-term avoidance of an allergenic/inflammatory trigger, in sensitized individuals, may be able to reduce long-term outcomes, also taking into account the possible additive effects of persistent inflammation. The key issue in this reasoning is whether effective allergen avoidance measures can be achieved. In this respect, intensive avoidance, long-term studies are awaited.

3.2 Pharmacotherapy

Early pharmacologic interventions are another option for controlling disease severity, reducing inflammation, and for consideration as a potential "allergic march-halting" strategy. The main pharmacologic approach for pediatric AR includes non-sedating antihistamines (mainly oral), topical nasal glucocorticosteroids, and an oral leukotriene receptor antagonist (LTRA).

Oral H_1-antihistamines (H_1-receptor inverse agonists) represent the first-line treatment for AR [1]. Their additional anti-inflammatory effect in nasal allergic inflammation has emerged in a number of studies: in children terfenadine [38] and cetirizine [39] reduced inflammatory cell infiltrate and intercellular adhesion molecule (ICAM)-1 expression on nasal epithelial cells, fexofenadine modulated the expression of leukocyte function-associated antigen (LFA)-1 and ICAM-1 on eosinophils [40], induced eosinophil-apoptosis [40] and attenuated eosinophil-mediated release of IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and soluble ICAM-1 from nasal epithelial cells [41]. Although histamine is a proven asthma mediator, H_1-antihistamines have rather inconsistent effects in asthma challenge models, BHR, and symptoms of perennial and seasonal asthma. Studies indicate that cetirizine [42] and loratadine (plus pseudoephedrine) [43] in recommended doses exert beneficial effects on seasonal AR patients with mild asthma symptoms. In an older meta-analysis of studies involving antihistamine use in persistent adult asthma, the beneficial effects noticed were found to be out-weighed by adverse effects [44]. Some H_1-antihistamines have demonstrated anti-inflammatory properties in the bronchial mucosa. Indeed, in a study of allergic untreated asthmatics who were allergen-inhalation challenged, Rédier et al. [45] observed lower bronchoalveolar lavage inflammatory (mainly eosinophils) cell numbers in the cetirizine versus the placebo pretreated. No significant clinical modification in the allergen inhalation-challenge test was observed. Even though the bronchodilator and bronchoprotective H_1-antihistamine effects are inconsistent, promising preliminary evidence on delaying the onset of infant asthma have emerged. These outcomes derive from randomized, double-blind, placebo-controlled studies of 1–3 years' duration, based on the administration of cetirizine [46] or ketotifen [47, 48] to infants at high risk of asthma development. It is, therefore, tempting to speculate that inhibiting the upregulation of adhesion molecules may prevent inflammatory cell migration into the airway and thereby may retard or even prevent the development of asthma [49]. Unfortunately, these findings were not confirmed in a similar levocetirizine study [50]. In conclusion, H_1-antihistamines only appear to contribute to the relief of mild seasonal asthma symptoms in patients with concurrent AR. Taking into consideration the important "systemic inflammatory dissemination" link in respiratory allergy, the fact that some H_1-antihistamines have proven additional anti-inflammatory effects, and the above-mentioned intriguing, but not confirmed, prevention findings, one can speculate that well-designed studies, possibly with new molecules, still hold promise as secondary asthma prevention measures in children with 'early' diagnosed AR.

Meanwhile, recent antihistamine research has focused on H_4-antagonists; the H_4-receptor seems important for the chemoattraction of immunologically relevant cells (eosinophils, mast cells, neutrophils, T-cells, dendritic cells) [51], making H_4-antihistamines promising in potentially modulating the pro-allergic function of these cells [52, 53].

Glucocorticosteroids are the most effective drugs when administered topically in the nose and the bronchi for the treatment of AR and asthma, respectively. Intranasal corticosteroids are more effective than antihistamines and the use of new, selective formulations with less bioavailability is not associated with growth retardation or other significant systemic side effects in children [54–56]. AR treatment using corticosteroids was found to improve asthma at best moderately, in some but not all studies. Reviews [57, 58] of the corresponding literature point out a non-significant tendency in asthma symptom and forced expiratory volume in 1 second (FEV_1) improvement. The findings on BHR are inconsistent as well. Ozturk et al. [59] reported that triamcinolone nasal spray blocked methacholine BHR increase after high-load natural pollen exposure in children with seasonal AR. On the contrary, Thio et al. [60] found no BHR effects of intranasal fluticasone and beclomethasone in children and young adults with seasonal AR and mild asthma. Yet, corticosteroid treatment of concomitant AR in asthmatics is associated with significant risk-reduction in asthma emergency room visits and hospitalizations [61]. Watson et al. [62], exploring the effect in the lower airways of treating AR with intranasal corticosteroids, showed that less than 2 % was deposited in the chest area. Since intranasal corticosteroids have not been shown to result in significant deposition to the lungs, the reduction in asthma symptoms may be related to improvements in nasal function rather than any direct effects of the medication on the lower airway [63]. Meanwhile, studies in children and adolescents demonstrate an efficient control on AR and asthma symptoms by simultaneous treatment with intranasally inhaled corticosteroids (budesonide [64], beclomethasone [65], fluticasone [66, 67]). Less is known about the effects on nasal disease of inhaled (intrabronchial) corticosteroid treatment [1]. In adults with seasonal AR without asthma, a study [68] examining the effects of inhaled budesonide on their AR concluded that in addition to nasal symptoms it also ameliorated the seasonal increase in blood and nasal eosinophils, and eosinophil cationic protein nasal lavage levels. If the systemic and nasal treatment effects in this study are due to pulmonary absorption of budesonide [68], these data suggest that inhibition of allergic eosinophilia could be interpreted towards an inhibition of the allergic march. Still, one can't disregard discouraging study outcomes pointing out that early use of inhaled corticosteroids for wheezing preschoolers had no effect on the natural history of asthma/wheeze later in childhood, and did not prevent lung function decline or reduce airway reactivity [69–71]. These findings don't provide support for a disease-modifying effect of inhaled corticosteroids after the treatment is discontinued. The fact that such medications need to be administered for long periods of time makes potential side effects a major disadvantage. The same stands for the use of *per os* corticosteroids and should be pointed out that, although short courses of prednisolone are occasionally administered in poorly controlled pediatric AR, the few corresponding studies in adult seasonal AR implicate effectiveness only in high (30 mg/day) doses [72].

Recently, a novel therapeutic intranasal combined formulation of azelastine and fluticasone propionate has demonstrated superiority over the sole administration of these agents in seasonal AR [73]. This high efficacy is auspicious as a potential "allergic march-halting" intervention but more studies are awaited.

Montelukast, an LTRA initially developed as a treatment for asthma, has also found use in AR. Systematic reviews and meta-analyses of randomized controlled trials on the effectiveness of LTRA, mainly in adults with seasonal AR, concluded that montelukast is modestly better than placebo, as effective as antihistamines, but less effective than nasal corticosteroids in improving symptoms and quality of life [74–76]. In combination with antihistamines (loratadine, cetirizine, or fexofenadine), montelukast has generally resulted in higher efficacy than when these agents were used alone [75–77]. A randomized, double-blind placebo-controlled study in children with seasonal AR reported that montelukast provides substantial improvement in symptoms and peripheral eosinophil counts; however, it didn't show a significant effect on eNO levels [78]. Besides this small but favorable study, the rest of the literature's endpoints are primarily on individual upper respiratory symptom scores and less on objective measures of the severity of concomitant asthma [76]. In one of the few double-blind, placebo-controlled, parallel-group multicenter studies on children with seasonal allergen sensitivity, montelukast over a 3-week treatment during the allergy season didn't significantly improve FEV_1 [79]. Taking into account the modest effects, as well as the negative results on the natural history of wheeze [80], the chances for montelukast to prevent the development of asthma in children with AR, although not evaluated, appear not very high.

3.3 Allergen-Specific Immunotherapy

Allergen-specific immunotherapy (SIT) is an important treatment modality and has been positioned as the only one that may alter the natural course of an allergic disease [34]. Currently, as far as AR is concerned, SIT is indicated in moderate/severe AR that doesn't respond to conventional

pharmacotherapy and allergen avoidance measures [81]. Scientific evidence of the efficacy of subcutaneous immunotherapy (SCIT) in AR have been demonstrated to a great extent in adults. Due to the plasticity of the pediatric immune system, the long-term benefit in children might be expected to be even better [34]. In one open study [82–84] in children with seasonal rhinoconjunctivitis, SCIT with grass and/or birch standardized allergen extracts for 3 years showed long-term (≥7 years) clinical effects and a preventive effect on asthma development. These possible protective and disease-modifying effects of SCIT indicate it may be favorable to start early in the disease process, even in children with well-controlled allergic symptoms [34]. However, this is yet to be substantiated. Regarding sublingual immunotherapy, some randomized controlled open trials in children have also suggested a preventive asthma effect [85–87]. As the quality of pediatric evidence in this area is not optimal, there is a need for well-designed, double-blind, placebo-controlled studies to assess the long-term immunotherapy effects in childhood [88]. The ongoing GAP (Grazax Asthma Prevention) trial represents the first double-blind, placebo-controlled randomized study aiming to assess the preventive effect of SIT on asthma development [89]. Last but not least, it must be kept in mind that the mechanisms leading to the disease-modifying effect, as well as the characteristics of patients particularly responsive to treatment, remain unclear.

3.4 Other Interventions

Over the last decades, the greater understanding of the pathogenesis of allergic diseases has led to the development of a number of novel targeted therapeutic approaches using biologicals. Among these, omalizumab, a humanized monoclonal antibody that binds circulating IgE and prevents its attachment to high-affinity IgE receptors, is the most extensively studied agent approved for the treatment of severe uncontrolled asthma with perennial sensitizations. However, a growing number of reports indicate its effectiveness in seasonal and perennial AR in adults/adolescents [90–94] and children [95–99]. Targeting the early phase of the allergic cascade could prove a significant allergic march-preventing treatment. The long-term effects of omalizumab are unknown, although there are reported observations of persisting efficacy [100, 101]. The high cost and some rare side effects [102] could be drawbacks.

The characteristic eosinophilic inflammatory response in AR could be approached by other novel, but yet off-label, biologicals. Mepolizumab, which blocks the binding of IL-5 to eosinophils, has shown a beneficial effect on severe eosinophilic asthma [103, 104], hypereosinophilic syndrome [105], and severe eosinophilic polyposis [106] in adults. Pitrakinra, a recombinant IL-4 variant that competitively binds the IL-4Rα receptor, inhibiting the binding of both IL-4 and IL-13, substantially diminished asthma symptoms during the late-phase asthmatic response after allergen challenge [107]. Studies of efficacy versus safety are ongoing; however, even if these two biologicals get approved in adults, evidence-based authorization for children should not be expected soon.

Another experimental approach in AR treatment is through the administration of probiotics. Some controlled trials reported overall positive results with the administration of lactobacillus in children with AR [108, 109], and a small study reported clinical and anti-inflammatory effects provided by *Bacillus clausii* [110]. Data showing that probiotic supplementation modulates immune responses in AR and may potentially alleviate the AR symptom severity [111] are encouraging, but their primary preventive effect on atopic diseases, probably by enhancing the T helper type 1 (TH1) response, is still unconfirmed [112].

4 Conclusion

There is currently little proof that allergen avoidance or pharmacotherapy may be able to affect the long-term natural history of respiratory allergy. Nevertheless, there is still scope for identification of responsive phenotypes, longer-term studies, and/or more intensive/focused therapeutic interventions, which may result in clinically relevant preventive effects. Furthermore, short- to medium-term effects on asthma outcomes may be achievable through AR treatments. Much more promising is the field of SIT, where current evidence, although not yet of ideal robustness, point towards a disease-modifying effect. Controlled studies, some already underway, are needed to describe this effect in detail. Finally, specific targeting of allergy mediators through biologicals is currently taking its first steps towards the clinic, initially targeting symptoms, but eventually expected to be evaluated in long-term studies.

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