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Preventing the development of asthma stopping the allergic march

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Abstract

Purpose of review: To describe important precipitants of asthma and allergic disease, to highlight the links between these triggers and modifications within the immune system, and to examine innovative research regarding asthma prevention with focus on attenuating the atopic march.

Recent findings: Allergen avoidance, allergen immunotherapy, IgE antagonists, prevention and treatment of respiratory infections, as well as management of gastrointestinal and respiratory dysbiosis have been considered as strategies in asthma prevention. Antenatal vitamin D supplementation in expectant mothers and aggressive control of atopic dermatitis (AD) to prevent the development of other allergic conditions were carefully studied as well.

Summary: Asthma is a major cause of morbidity and lost productivity. Despite the tremendous burden of this disease, the scientific community is still struggling to find an effective means of prevention. The contribution of genetics to the development of atopy cannot be altered, but environmental changes as well as pharmacotherapy have been studied as modifiable risk factors. Many trials to date have been effective only for subjects with certain characteristics. This is likely because asthma is a heterogenous condition, with a variety of triggers and clinical phenotypes. Thus far, a universally effective prevention strategy has eluded us. However, once confirmed, an intervention to prevent asthma and the allergic march will improve quality of life for millions of sufferers and decrease health care expenditures.

Keywords

atopy; asthma; sensitization; prevention; immunotherapy

Introduction

Asthma affects approximately 300 million people globally, and represents the most common non-communicable disease. It carries a disproportionately high impact on children, and

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nearly 6 billion dollars are spent annually due to pediatric asthma alone.[1] Its impact is growing exponentially—it has been suggested that there may be an additional 100 million people suffering from asthma by 2025.[2] The “atopic march” refers to IgE mediated allergic progression beginning with AD and food allergy in infancy, followed by aeroallergen sensitization in the preschool age, culminating in the development of allergic rhinitis (AR) and chronic asthma.[3] Preventing the inception of this allergic progression, as well as halting its advance, is pivotal in asthma prevention. Aggressive therapies in infants with AD,[4, 5] global blocking of allergic inflammation with daily inhaled steroids,[6] the role of allergic sensitization,[7, 8] immunotherapy,[9–16] respiratory infections,[17–20] and dietary interventions[21, 22] have been evaluated in asthma and atopy prevention. Biologic therapy for susceptible toddlers,[23] and modulation of the respiratory microbiome through killed bacterial lysates are being investigated. The influence of environmental factors, such as pollution, in asthma pathogenesis is well established.[27] Our ability to intervene upon these contributing factors can alter the course of the disease and is the focus of ongoing investigation.

Early Control of AD for Atopy Prevention

As the atopic march often begins with AD, children with this condition have been targeted in prevention studies. The Early Treatment of the Atopic Child study was a double-blinded, parallel group, randomized controlled trial of cetirizine administered twice daily over 18 months to children with AD, with 18 months of further follow-up. Overall the intervention group did not have a lower prevalence of asthma when compared with the placebo group, however, a specific subgroup of children, those sensitized to house dust mite (HDM) and/or grass pollen, were less likely to develop asthma while taking cetirizine. The preventative effect continued through the 18 month follow up period for those sensitized to grass.[5]

Another study considered whether intensive pharmacotherapy for control of AD could limit progression of the atopic march. The Study of the Atopic March was a prospective, randomized, double-blind, placebo-controlled, longitudinal study evaluating the use of pimecrolimus, a topical calcineurin inhibitor, in infants aged 3–18 months with AD. Children were followed for 3 years or longer, but there was no difference between intervention and control groups in the prevalence of asthma, or other allergic conditions.[4]

Inhaled Corticosteroids for Asthma Prevention

In the Prevention of Early Asthma in Kids cohort, preschoolers at risk of asthma were also found to have a high rate of aeroallergen sensitization.[28] Children determined to be at risk of asthma through the asthma predictive index[29] were then treated pre-emptively with two years of inhaled corticosteroids and followed one year after. While the intervention improved asthma control during treatment, it did not decrease burden or alter the progression of the disease after the therapy was stopped.[6]

Vitamin D

The intrauterine period may represent a critical window in the development of atopy and asthma. Data suggests that higher in utero 25-hydroxy-vitamin D confers protection against the development of asthma. 581 pregnant women were randomized to high dose vitamin D (either 2,400 or 4,000 I.U. daily) or placebo. There was a 25% reduced risk of asthma in the offspring of the treated mothers at 0–3 years.[30] Suboptimal levels of vitamin D may lead to impairment of various immune functions involved in asthma and allergic disorders. [31] However, most wheezing that occurs prior to age 3 is attributable to transient viral infection and not persistent asthma long term follow up of these studies is essential to determine if this therapy prevents the development of chronic asthma.[32]

Traffic pollution, in combination with allergen exposure, synergistically precipitates asthma exacerbations.[33, 34] Vitamin D may attenuate airway inflammation in the setting of pollution.[22] Exposure of infants to the 1952 Great Smog of London increased asthma rates by about 20%.[27] Bolcas and colleagues reported that vitamin D confers protection against asthma development in the setting of exposure to traffic related air pollution. Vitamin D replacement did not reverse established asthma, but maintenance of normal vitamin D status in childhood significantly mitigated the development of airway hyperresponsiveness in allergic asthma that was worsened by diesel exhaust. It is suggested that vitamin D reduces pulmonary Th2/TH17 cells, which portend the development of severe asthma.[22]

Modification of the Microbiome

The bacterial milieu has been studied in asthma pathogenesis, and modifying the microbiome is being targeted in asthma and atopy prevention. Broncho-Vaxom is an oral immunomodulator containing a bacterial lysate of pathogenic respiratory bacteria which can stimulate immune defenses and is used to prevent recurrent infections. A recent metanalysis involving 4851 pediatric patients, confirmed that its administration significantly reduced the frequency of respiratory infection.[35]

However, the data behind the use of bacterial lysates for atopy prevention varies. In one mouse model of asthma, oral administration of Broncho-Vaxom attenuated airway inflammation as measured by airway wall thickness, luminal stenosis, mucus plugging and eosinophilic infiltration.[25] Conversely, in another murine model, Broncho-Vaxom did not reduce pulmonary eosinophilic response, or improve lung resistance, but did decrease IL-5 and IL-13 in bronchoalveolar lavage fluid.[26] A clinical trial, Oral Bacterial Extract for the Prevention of Wheezing Lower Respiratory Tract Illness (ORBEX), NCT02148796, is currently underway, to assess the efficacy of killed bacterial lysates in asthma prevention. [36]

Probiotics

Probiotics have been evaluated in the prevention of atopy. Strains of lactobacilli and bifidobacteria are the most commonly employed for the prevention of allergic disease.[37] A large meta-analysis of 2403 studies showed that probiotics may prevent AD, but not prevent other allergic conditions.[38] However, another randomized, prospective, double-blinded controlled trial did not show probiotics decreased AD or asthma risk at age two.[39]

Avoidance of Allergic Sensitization

Allergic sensitization plays an integral role in atopy pathogenesis and progression, especially with regards to asthma.[40] Recent population level studies in the US have indicated that almost half of the US population is sensitized to aeroallergens and that exposure to multiple allergens in homes is common.[41] A study from the 1960s showed that the presence of allergic sensitization and AR significantly decreased the likelihood that a child would outgrow his asthma by age 16. This indicates that allergic sensitization is a critical step in asthma development.[42] In a 2017 study, 127 infants hospitalized or seen in the ED for first severe wheeze, were followed to determine asthma prevalence at 8 years. The 17% who were sensitized to allergens at the time of study entry (median age 11 months) had a 12 times higher risk of developing atopic asthma by age 8 than their non-sensitized counterparts.[20]

Information from the Childhood Origins of ASThma (COAST) cohort informs the relationship between allergen exposure and asthma development. Allergen specific IgE was measured at four intervals between 1 and 9 years of age, in a population at high-risk for asthma development. Sensitization to specific perennial allergens, like cat and dog, was highly associated with asthma risk. Interestingly, dog exposure at birth was associated with a reduced risk of asthma, irrespective of sensitization status.[40] Specific gene-environment interactions such as the effect of pet exposure on those with a high risk variant in the chromosome 17q21 locus, may modify the relation between pet exposure and asthma in at-risk individuals.[43] Recent analyses suggest that clusters of exposure combined with specific sensitization can augment asthma risk, highlighting the complexity of this progression.[44, 45]

Given the critical role that allergic sensitization plays in the development of atopy, allergen avoidance was studied as a means of prevention. In the Isle of Wight prevention study, infants at high risk of atopy were randomized to an intervention group that included breastmilk by a mother on a low allergen diet or hydrolyzed formula, with reduced exposure to HDM or to a control group without intervention. A significant decrease in asthma, AD, rhinitis and atopy was seen in the prevention group.[7] At age 18, asthma was still less prevalent in those who had received the intervention. However, the prevalence of atopy and allergic sensitization had equalized.[8] While this study showed that allergen avoidance had a preventative effect, other studies have been equivocal or shown an increase in atopy (Table 1). Allergenic and microbial exposures are complex,[46] making the practical implementation of these avoidance measures difficult.

Allergen Immunotherapy

Aside from allergen avoidance for the prevention of asthma and atopy, targeting allergic sensitization through immunotherapy, has been studied in the prevention of asthma and atopy in several controlled trials (Table 2). [9, 12, 13, 15, 16, 47] The role of immunotherapy in prevention of new sensitization as well as in mitigation of asthma symptoms has been appreciated since the 1960s.[48] Immunotherapy can improve the likelihood that a known asthmatic will outgrow his asthma.[42] Several randomized controlled trials have

demonstrated that immunotherapy minimizes new allergic sensitization in individuals already sensitized to other allergens, but its effect on asthma prevention has varied.[13, 15, 47]

In a prospective, randomized controlled study, Jacobsen and colleagues evaluated 3 years of subcutaneous immunotherapy (SCIT) in children with seasonal AR and found that at 10 years, allergic rhinoconjunctivitis along with reported asthma rates were significantly lower in the SCIT group, as compared with those who did not receive immunotherapy.[9] The study had several limitations: it was not blinded, and while reported diagnoses of asthma were statistically significant, bronchial hyperresponsiveness as measured by methacholine challenge was not significantly different between the two groups.[9]

Sublingual immunotherapy (SLIT) has been extensively studied for asthma and atopy prevention.[12, 13, 15, 16] In one prospective, randomized controlled, proof of concept study in infants at high risk of atopy, the intervention group was treated with HDM oral immunotherapy, twice daily for one year, while the control was treated with placebo. While the study confirmed decreased sensitization to common allergens in the intervention group, there was no effect on the development of AD, food allergy, or wheeze.[47] Another open, randomized controlled trial was more promising. This study involved 113 children between ages 5 and 14 with AR who were sensitized to grass. The intervention arm received three years of grass SLIT and the control group received standard medical therapy. The control group had a four-fold increased rate of asthma as compared with the group who received immunotherapy, suggesting that immunotherapy may have a protective effect against asthma development.[15]

In patients sensitized to HDM who were treated with SLIT, spirometry and bronchoprovocation via methacholine were studied and confirmed that SLIT, over a 5-year period, had a significant protective effect on pulmonary function, as compared to a control group of sensitized individuals who did not receive immunotherapy.[12] Furthermore, a recent metanalysis evaluated allergen immunotherapy in those with AR and found a statistically significant reduction in the development of asthma in the two years following completion of immunotherapy. [11] It is unclear if this benefit is pervasive.

The mixed results from these trials indicate that immunotherapy may be helpful in the prevention of asthma and atopy, but more research is needed to help determine which patients will benefit, and for how long. Immunotherapy interferes with the pathophysiology that mediates allergic and asthmatic disease, and can potentially impact the progression of atopy over the long-term. One proposed mechanism is that immunotherapy induces specific IgG4 which reduces late-phase airway hyperreactivity and mitigates allergic inflammation.[10]

Prevention of Respiratory Infections

There is robust data that allergic sensitization and viral infection interact synergistically in the pathogenesis of asthma. Allergic sensitization, particularly to HDM and mouse, combined with early-life rhinovirus infection compounds the risk of developing asthma and also increases asthma severity. This suggests that IgE may play a significant role in modifying asthma severity. Genes underlie a predisposition to sensitization, while exposure

to allergens, respiratory infections, and pollution may modify asthma severity seen among individuals.[19]

More than 80% of asthma exacerbations are triggered by respiratory viral infections, and two-thirds of these are attributable to rhinovirus, which also increases asthma severity.[19] It is postulated that rhinovirus disrupts the airway epithelium, upregulates IL-25 and IL-33, and catalyzes type 2 airway inflammation and remodeling.[18] Limiting the pulmonary inflammation ignited by rhinovirus is a possible intervention point in stymying the progression of transient wheeze to asthma. Omalizumab may be helpful in this regard.[49]

Omalizumab for atopy and asthma prevention

Omalizumab (Anti-IgE) has been shown to significantly decrease asthma related symptom days, fall and spring exacerbations, hospitalizations, and need for inhaled corticosteroids.[50] In the Preventive Omalizumab or Step-up Therapy for Fall Exacerbation (PROSE) study, treatment with omalizumab also decreased the risk and duration of rhinovirus infections, and minimized viral shedding. By antagonizing IgE, omalizumab may limit both the allergic and virally-induced airway inflammation that underscores asthma pathogenesis and play an advantageous role in prevention.[50] Mechanistically, blocking IgE may inhibit the allergic sensitization that mediates asthma pathogenesis. Additionally, the cross-linking of IgE may restore virus induced IFN-alpha responses, which are often lacking in asthmatic patients.[51]

Given omalizumab's benefit in asthma and its underlying mechanism of blocking IgE, as well as alleviating the burden of rhinovirus, omalizumab is under consideration as a therapy for asthma prevention and disease modification. Pre-school is considered a "critical period" in the maturation of the immune and pulmonary systems. The Preventing Asthma in High Risk Kids study (NCT02570984) is currently underway to determine whether 2 years of omalizumab therapy in predisposed preschoolers can prevent asthma development.[23]

Conclusion

The concept of the "allergic march" as a progression has recently been called into question, as more than 90% of children do not follow the typical trajectory. However, the contribution of atopic sensitization to these disorders is paramount.[52] Furthermore, asthma is a heterogenous entity, influenced by both genetic and environmental factors. These make finding a "one-size fits all" prevention strategy a challenging task. Tang and colleagues recently reported on 3 distinct trajectories of asthma, one higher-risk, atopic cluster, and two lower risk clusters more prone to transient wheeze, including one non-atopic subgroup and one group susceptible to non-atopic and atopic wheeze.[45] Each cohort may require different strategies for prevention. In the future, genetic variations among susceptible individuals with distinct asthma phenotypes, may help target prevention strategies in a more precise manner. Currently, we know that allergic sensitization combined with early life viral infections synergistically regulate asthma development and severity.[19]

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Key Points

1. Vitamin D and probiotics may be helpful in preventing allergic disorders, but currently their benefit seems to be limited to certain populations and at specific times. More research regarding their use for prevention of atopy in the general population is needed, with focus on prospective studies with long term follow up, which is lacking in the current literature regarding these supplements.
2. Allergic sensitization plays an integral role in asthma pathogenesis.
3. There is a synergistic effect between allergic sensitization and viral infection in the development of asthma, and IgE likely plays a causal role in regulating asthma severity.
4. Prevention of allergic sensitization and improved anti-viral immunity during the toddler years, a critical period for immune as well as pulmonary development, may be helpful in preventing asthma. Omalizumab may be helpful in this capacity, and is being studied for asthma prevention.

Table 1:

Select studies evaluating the association between allergic sensitization and asthma development

Reference	Population	Study Design	Intervention	Other Clinically Relevant Outcomes	Asthma-Related Outcome
Cullinan et al. (2004)[53]	625 children followed from birth to age 5.5 years	Prospective cohort study	Der p 1 and Fel d 1 allergens measured in homes at 8 weeks of life. Annual interview regarding wheeze. SPT completed at 5.5 years.	10% sensitized to HDM or cat. No relation between allergen exposure and sensitization or wheeze found.	7% had atopic wheeze. Risk of asthma rose at low exposure level and then was attenuated thereafter.
Marks et al. (2006)[54]	616 children with family history of asthma were randomized antenatally and followed through the first 5 years of life	Prospective RCT	*Intervention 1*: HDM avoidance vs control *Intervention 2*: Dietary modification vs control.	HDM avoidance resulted in a decrease in HDM in the child's bed.	No significant difference in the prevalence of asthma in the HDM avoidance group.
			Assessed for asthma and eczema and had skin prick tests for atopy at age 5.	No significant difference in the prevalence of eczema, or atopy.	
Arshad et al. (2007)[7]	120 infants recruited prenatally from atopic families	Prospective single-blind RCT	*Intervention (n=58)*: Infant Breast-fed by mother on low allergen diet or given extensively hydrolyzed formula. HDM exposure reduced by acaricide and mattress covers. *Control (n=62)*: Standard advice	At age 8, statistically significant decrease in allergic sensitization to foods as well as HDM, AR, AD and atopy in the intervention group.	At age statistically significant decrease in asthma
	Study focused on limiting food and HDM exposure				
Scott et al. (2012)[8]	120 infants recruited prenatally from atopic families	Prospective single-blind RCT	*Intervention (n=56)*: Infant Breast-fed by mother on low allergen diet, or given extensively hydrolyzed formula. HDM exposure reduced by acaricide and mattress	At age 18, no difference in allergic sensitization to foods as well as HDM, or atopy in the intervention group.	At age statistically significant decrease in asthma

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			covers. *Control (n=58)*: Standard advice		
	Study focused on limiting food and HDM exposure				
Stoltz et al. (2013)[40]	High-risk children for development of asthma and allergy enrolled in the COAST study	Prospective longitudinal cohort study	Specific IgE measured at 1, 3, 6 and 9 years. Current asthma and AR diagnosed at 6 and 8 years	Sensitization to seasonal allergens more associated with rhinitis risk.	Sensitization to cat and dog associated with increased asthma risk. Sensitization to perennial versus seasonal allergens also associated with asthma risk. Dog exposure at birth associated with decreased asthma risk, regardless of sensitization.
Belgrave et al.(2018)[55]	1046 patients from ages 5–24 from MAAS and ALSPAC cohorts followed with spirometry to ascertain trajectories of FEV1	Prospective longitudinal cohort study	Factors influencing FEV1 were studied in these two cohorts	Participants with recurrent severe wheeze exacerbation by age 3 years (p=0.048) and allergic sensitization at 3 (p=0.017) had increased likelihood of belonging to the subgroup of persistently low FEV1	

Abbreviations-- IT: Immunotherapy, SLIT: Sublingual immunotherapy, SCIT: Subcutaneous immunotherapy, SPT: Skin Prick Test, AR: allergic rhinoconjunctivitis, RCT: Randomized controlled trial, HDM: House dust mite, FEV1: Forced expiratory volume in one second. MAAS: Manchester Asthma and Allergy Study, ALSPAC: Avon Longitudinal Study of Parents and Children

Table 2:

Selected studies evaluating the role of immunotherapy in the prevention of atopy and asthma

Reference	Population	Study Design	Intervention	Other Clinically Relevant Outcomes	Asthma-Related Outcome
Johnstone DE and Crump L. (1961)[48]	200 children sensitized to inhalants, age 0–15, with perennial bronchial asthma	Prospective randomized controlled, double-blinded	*Each therapy given for 4 years. Control (n=42)*: SCIT with buffered saline. *Intervention 1 (n=49)* SCIT 1/10,000,000 weight by volume to all sensitized inhalants based on SPT. *Intervention 2 (n=39)*: SCIT 1/5,000 dilution of all sensitized antigens *Intervention 3 (n=43)* highest tolerated dose of SCIT, up to 1/250 dilution.	None of the children in Intervention groups 2 or 3 developed new sensitizations while on immunotherapy	At study completion, 64% of the control group displayed wheezing on exertion, while only 9% of those receiving the highest tolerated dose of immunotherapy displayed wheeze with exertion.
Johnstone DE and Dutton A (1968)[42]	210 children with perennial AR and bronchial asthma were assessed at age 16 for continued asthma symptoms	Prospective randomized placebo-controlled study	The same interventions as above.	Only 12 of 73 children had asthma develop prior to AR. Presence of AR during childhood significantly lessened the likelihood that a child in this study would outgrow asthma by age 16.	22% of placebo-treated children were symptom free, while 72% of treated children were symptom free. (66% of the 1/5000 group, and 78% of the highest tolerated dose group were symptom free.)
Novembre et al. (2004)[15]	113 children aged 5–14 years with AR and grass allergy, but no prior signs of asthma	Prospective randomized open controlled study	*Intervention (n=54)*: Treated with grass SLIT for 3 years *Control (n=59)*: Standard pharmacotherapy	Treated children had reduced symptoms and used less medication in the second and third years.	There was a four-fold increased rate of asthma development in the children allergic to grass and not treated with IT.
Jacobsen et al. (2007)[9]	147 subjects, aged 16–25 years, with grass +/− birch pollen allergy	Prospective open, partially RCT	*Intervention (n=64)*: SCIT with standardized birch +/− grass pollen extracts for 3 years. *Control (n=53)*: Standard medical therapy for allergic rhinoconjunctivitis	AR in SCIT group improved significantly more than pharmacotherapy group	10 years later those treated with SCIT had a statistically significant lower rate of asthma than those in the control grou
Marogna et al. (2010)[13]	78 adult patients, aged 18–65, all monosensitized to HDM	Prospective open, RCT	*Intervention 1 (n=19)*: SLIT to HDM for 3 years *Intervention 2 (n=21)*: SLIT to HDM for 4 years *Intervention 3 (n=17)*: SLIT to HDM for 5 years *Control (n=21)*: pharmacotherapy alone	In Intervention groups, new sensitizations developed in only 21%. In intervention group 1, benefit persisted for 7 years. Intervention groups 2 and 3 had benefit for 8 years. No change in control group, over 15 years, new sensitizations developed in 100%.	
Zolkipli et al. (2015)[47]	111 infants <1 year old at high risk of atopy, but not yet sensitized	Prospective, double blind, RCT	*Intervention (n =57)*: HDM extract given orally twice daily for 12 months *Control (n =54)*: Placebo administered orally	Sensitization to any common allergen 25.5% in control group and only 16% in the intervention group. No effect on AD, or food allergy.	SLIT had no significant preventative effect on wheeze.

Reference	Population	Study Design	Intervention	Other Clinically Relevant Outcomes	Asthma-Related Outcome
			twice daily for 12 months		
Marogna et al. (2017)[12]	142 patients (age 8–57) with AR, monosensitized to HDM	Prospective open, non-randomized, controlled	*Intervention 1 (n=41)*: Adjuvanted SLIT (Bacterial wall derived adjuvants, that engage TLRs) *Intervention 2 (n=43)*: Standard SLIT *Control (n=40)*: Pharmacotherapy only	After 5 years of treatment, 58% of the control group developed new sensitizations, while 13.2% in the standard SLIT group did and only 8.1% in the adjuvanted group did. Patients treated with SLIT used less medications.	Patients in the control group had a decline in FEV1 over the 5 years of the study, while those treated with IT had stable FEV1.
Valovirta et al. (2018)[16]	812 children, aged 512 years with AR caused by grass pollen, but no medical history or signs of asthma	Randomized , double-blind, placebo-controlled trial,	*Intervention (n=398)*: 3 years of treatment with grass SLIT *Control (n=414)*: Placebo tablets	Use of AR pharmacotherapy was significantly less in the intervention group. Total IgE, grass pollen specific IgE and SPT reactivity were reduced in the intervention group.	Treatment with grass SLIT in sensitized individuals reduced the risk of experiencing asthma symptoms or using asthma medications at the end of the trial, which was a total of 5 years. Did not significantly prevent asthma.

Abbreviations-- IT: Immunotherapy, SLIT: Sublingual immunotherapy, SCIT: Subcutaneous immunotherapy, SPT: Skin Prick Test, AR: allergic rhinoconjunctivitis, HDM: House dust mite, FEV1: Forced expiratory volume in one second.