

Prevention of asthma in childhood

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Purpose of review

The prevalence of asthma is increasing in many parts of the world, particularly in developed countries. The present review focuses on recent literature regarding asthma prevention in childhood.

Recent findings

Several environmental exposures in infancy or early childhood are associated with reduced prevalence of asthma, but the mechanisms leading to these associations remain unknown. Recent studies have demonstrated limited success in the prevention of asthma or asthma symptoms with the use of asthma medications, once the therapy is discontinued. Immunotherapy offers another strategy for asthma prevention, and groups treated with this intervention have demonstrated reduced atopy and asthma. Several multi-interventional trials have demonstrated a reduced asthma symptom burden but have not demonstrated significant differences in objective measures such as lung function or bronchial hyper-responsiveness between intervention groups.

Summary

The most promising asthma prevention strategies to date have been those that use a multi-interventional approach employing both dietary and environmental manipulations. More research is needed to assess the long-term follow-up of multi-interventional trials and to evaluate novel intervention strategies in the primary or secondary prevention of asthma in childhood.

Keywords

asthma, childhood, prevention, wheezing

Introduction

The prevalence of asthma has increased over the past two decades in many parts of the world [1]. Studies of the natural history of asthma have demonstrated that the majority of people with asthma begin demonstrating signs of the disease within the first 6 years of life [2]. This review focuses on recent findings with regard to environmental risk factors, medication trials, immunomodulatory interventions, and multi-interventional strategies in the prevention of asthma in childhood. Prevention can be thought of as either primary or secondary. Primary prevention strategies are those that promote immune development away from a proasthmatic response. Secondary prevention strategies target high-risk infants or children in which manifestations of the disease have already occurred, to decrease the morbidity of the disease and prevent damage to the developing pulmonary system.

Environmental

As noted earlier, there has been an increase in the prevalence of asthma in the past two decades, which has been attributed to environmental and lifestyle changes as there was not sufficient time for a genetic mutation to be observed. It has been postulated with the 'hygiene hypothesis' that exposure to certain infections and vaccines might alter the immune response away from the development of atopy [3,4]. Several studies have demonstrated the association of reduced atopic disease in children exposure to large amounts of microbial products in the environment during infancy and early childhood, and a modest decrease in the prevalence of asthma with allergen avoidance measures.

Farm

Large cohorts of children from several European countries demonstrated that children who lived on a traditional farm having regular contact with livestock were less likely to suffer atopy and asthma [5–7]. These studies described the protective effect of early-life environmental exposures such as microbial products from livestock against the development of atopy and asthma.

Pets

A systemic review of the impact of pet ownership on the subsequent development of asthma has demonstrated that in children younger than age 6 years exposure to pets was associated with a decreased risk for asthma and wheezing. Pet ownership over the age of 6 years increased the asthma risk [8]. The presence of at least

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Abbreviations

HDM house dust mite
ICS inhaled corticosteroids

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one dog in the household in the Tucson Children's Respiratory Study conferred a decreased risk of subsequent wheezing but not atopy [9]. Maternal history of asthma may also alter this relationship – those children with a mother with a history of asthma, and exposure to cats demonstrate a significantly increased risk of wheezing [10]. A cohort study from The Netherlands showed borderline significant associations between cat allergen exposure and persistent wheeze in the total study population and between dog allergen and persistent wheeze in children of nonatopic mothers [11]. To date, the association of pet exposure and atopy is not consistent.

Sibs and daycare

A study of East German children placed in daycare in preschool years found the earlier children from small families entered daycare, the less the prevalence of atopy [12]. The Tucson Children's Respiratory Study demonstrated that children who attended daycare during the first 6 months of life, or those children with older siblings, were less likely to have asthma than children who did not [13].

Unpasteurized milk

Children exposed to farm stables and/or unpasteurized milk during the first year demonstrated protection against the development of asthma and allergic sensitization [7]. Prenatal exposure also had a substantial protective effect [7].

Breast-feeding

Results have been conflicting on whether breast-feeding confers a protective or increased risk on the development of asthma and atopy. Many studies have shown a protective effect of breast-feeding against asthma and atopy [14–18]. Wright and colleagues [19], however, reported breast-feeding to be associated with an increased risk of asthma, particularly in those children with a maternal history of asthma and personal history of atopy, and Sears *et al.* [20] described an increased risk of asthma if breast-fed that was not changed by a family history of atopy. This story is still evolving and breast-feeding should still be encouraged given its numerous other benefits.

Allergen avoidance

Three recent studies have examined the primary prevention strategy of house dust mite (HDM) avoidance measures started before birth, such as reducing indoor humidity, using an allergen-impermeable mattress and pillow covers, and washing bedding in hot water. The study of prevention of allergy in children in Europe recruited three cohorts of newborns [21], of toddlers [22], and of school-aged children [23] with a family history of atopy for the primary prevention of HDM sensitization and asthma. In the newborn group, sensitization was decreased at 1 year but the difference was lost by age 2. In the toddler and school-aged cohorts, a reduction in the incidence of HDM sensitization was observed at 1 year but not in the occurrence of allergic manifestations. The Prevention and Incidence of Asthma and Mite Allergy study in The Netherlands looked at the effect of HDM avoidance measures on the children's and parents' beds before birth and during the first year of life. Although HDM allergen levels were reduced in the intervention group [24], there was no difference in the development of atopy or asthma. At age 2 years, only a small but significant decrease in night-time cough was observed in the children in the intervention group [25,26]. At 4 years of age, no significant difference was seen between the treatment groups in the outcomes of sensitization or atopy [27*]. The Manchester Childhood Asthma and Allergy prevention study used HDM avoidance measures on the parents' beds from the second trimester and on the child's bed after birth [28]. At age 1 year there was no difference in mite sensitization, mild wheeze, or cough or atopic dermatitis. There was a significant reduction in the occurrence of severe wheeze in the intervention group. Given the chronic nature of asthma, however, long-term follow-up of these studies is crucial to determining whether the positive effects of these interventions will be sustained.

The mechanisms associated with protective effects due to environmental exposures remain unknown. It is speculated that increased concentrations of bacterial components such as endotoxin present in farm or daycare environments may stimulate an immune response that protects the child from developing atopic disease [3].

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Medication trials

For the most part, medication trials have been designed as secondary prevention strategies targeting high-risk infants or children in which manifestations of the disease have already occurred. This is to avoid treating a large number of children that may outgrow their disease with medications that may have undesirable side effects.

Inhaled corticosteroids

The use of inhaled corticosteroids (ICS) in asthma prevention has been addressed in several studies published in the past 5 years. The Childhood Asthma Management Program [29] study involved 1041 children aged 5–12 years with mild to moderate asthma. These children were randomized into three groups to receive budesonide, nedocromil or placebo and were followed for 4–6 years [29]. No significant difference in the primary outcome of postbronchodilator lung function was observed between treatment groups. Bisgaard and colleagues [30*] studied the effects of intermittent ICS compared with placebo given for 2 weeks during wheezing episodes to infants with maternal history of

asthma and one episode of wheezing. At 3 years of age there were no significant differences between treatment groups in the proportion of symptom-free days and measures of specific airway resistance. In the Prevention of Early Asthma in Kids study, 285 high-risk children, 2 and 3 years old, were randomly assigned to treatment with an inhaled corticosteroid or placebo for 2 years [31^{••}]. The children were considered high risk if they had a positive modified asthma predictive index that included frequent wheezing and a history of familial or personal atopic risk factors [32]. The children were followed for an additional 12 months after discontinuation of study medication. During the treatment period, the inhaled corticosteroid group had a greater proportion of episode-free days, a lower rate of exacerbations, less supplementary use of controller medication, and improved measures of lung function compared with the placebo group. Shortly after the inhaled steroid was discontinued, there was no significant difference between groups in the measures of asthma burden or lung function. Murray *et al.* [33[•]] studied 200 infants with an atopic parent who were randomized to receive either ICS or placebo after their first episode of prolonged wheezing (>1 month) or two medically confirmed episodes of wheeze. At 5 years of age, there were no differences between treatment groups in the prevalence of doctor-diagnosed asthma, use of asthma medications, lung function or airway reactivity. Evidence suggests that although daily ICS improve the control of asthma, ICS do not alter the natural course of asthma in school-aged children and do not prevent development of asthma in high-risk preschool children.

Nasal steroids

One study reported no significant difference in seasonal bronchial hyper-responsiveness in a small group of non-asthmatic children with seasonal allergic rhinitis treated with nasal steroids and those treated with placebo [34].

Leukotriene receptor antagonists

Bisgaard [35] studied 130 infants aged 3–36 months who were hospitalized with respiratory syncytial virus. Montelukast or placebo was administered within 7 days of the onset of symptoms for a total of 28 days. Those infants treated with montelukast had significantly more symptom-free days (22% versus 4%, respectively) [35]. This observation that leukotriene antagonists may prevent the development of persistent asthma symptoms after respiratory syncytial virus bronchiolitis will need to be confirmed with larger longitudinal studies.

Antihistamines

The 'Early Treatment of the Atopic Child' study [36] randomized 566 children between 1 and 2 years of age with atopic dermatitis for at least 1 month and a positive family history of atopy. These children were given either

cetirizine or placebo for 18 months and were followed for an additional 18 months off study medication. Although there was no difference between study groups in the cumulative prevalence of asthma, a post-hoc analysis suggested that children with aeroallergen sensitization to dust mite or grass pollen treated with cetirizine were approximately 50% less likely to have asthma symptoms than those receiving placebo. The Preventia I study [37] randomized 412 children aged 12–30 months with no more than two episodes of wheezing but with frequent respiratory infections to treatment with loratadine or placebo, and the study found no significant difference in the number of respiratory infections or pulmonary exacerbations between treatment groups once the medication was stopped.

To date, there has been no demonstration that early intervention with medication has resulted in sustained differences in asthma burden or lung function later in life once the medication is stopped.

Immunomodulatory strategies

Strategies that modulate the immune system at an early age are ideal primary prevention candidates to promote immune development away from a proasthmatic response. These trials typically employ interventions in high-risk, young children with a positive family history and atopic manifestations to prevent the 'atopic march'.

Probiotics

Beneficial microbes in the gut flora may promote maturation of the immune system away from proatopic immune development. Kalliomaki and colleagues [38] studied 159 pregnant women with a family history of atopic disease and were given either oral *Lactobacillus rhamnosus* strain GG or placebo daily. After birth, the infants or breast-feeding mothers were continued on daily *Lactobacillus rhamnosus* strain GG or placebo. Significantly less infants developed atopic dermatitis by 2 years of age. A similar protective effect was recently found [39]. The effectiveness of *Lactobacillus* on the prevention of asthma, however, has yet to be studied.

Vaccine

Martignon and colleagues [40] examined a group of 718 unselected adolescents and found those who had been vaccinated had a significantly lower risk of asthma compared with those not vaccinated, after adjusting for possible confounding variables. Live attenuated vaccines conferred a greater protective effect.

Immunotherapy

A recent report also suggested that allergen-specific immunotherapy for 3 years in children aged 6–14 years with allergic rhinitis reduced the prevalence of new-onset

asthma in these patients after 3 years [41] and after 5 years [42]. A recent open study of 113 children aged 5–14 years with allergic rhinitis but with no more than three episodes of seasonal asthma who were sensitized to grass pollen were randomized to receive either sublingual immunotherapy or standard symptomatic therapy alone [43]. The development of asthma after 3 years was 3.8 times more frequent in the control individuals. A recent review concluded that sublingual immunotherapy is an effective treatment but several questions remain, such as the effective dose, treatment schedules, and the duration of treatment [44^{••}].

Anti-immunoglobulin-E

A total of 221 patients, 6–17 years of age, with a clinical history of seasonal allergic rhinitis were randomized to receive allergen immunotherapy and monoclonal anti-IgE or allergen immunotherapy alone [45]. The combination therapy group had a 48% reduction in allergic rhinitis symptoms compared with allergen immunotherapy alone, suggesting this as a promising area of study for asthma prevention.

The use of anti-IgE is an interesting area for future research, particularly when used in combination

with environmental manipulation or other types of medication.

Multi-intervention trials

Several studies have employed multiple interventions that include both dietary and allergen avoidance strategies in the prevention of asthma.

The Isle of Wight Prevention study

The Isle of Wight Prevention study evaluated the effect of a combined food and HDM allergen avoidance intervention in 120 high-risk infants with a family history of atopy from birth to age 1 year. Arshad and colleagues [46] demonstrated a sustained reduction in sensitization and the prevalence of asthma up to age 8 but no difference in bronchial hyperresponsiveness or lung function.

The Prevention of Atopic Allergy study

In this trial, 513 high-risk children with a positive family history were randomized to a reduction in food allergen with exclusive breast-feeding or soya formula and environmental exposure to HDM and environmental tobacco smoke intervention, or to a control group. The intervention group demonstrated significantly less

Table 1 Randomized controlled, multi-interventional studies with environmental avoidance and dietary measures^a

Study	Number	When intervention started	Intervention	Main outcome measures	Reported follow-up and outcomes showing significant reduction
Isle of Wight Prevention study [46,51–53]	120	Birth	Food and HDM allergen avoidance	Allergic sensitization Asthma Allergic rhinitis Atopic dermatitis Food allergy	HDM allergen levels 1 year: asthma, atopic dermatitis, and allergic sensitization 2 years: atopic dermatitis and allergic sensitization 4 years: atopic dermatitis and allergic sensitization 8 years: asthma and allergic sensitization
Prevention of Atopic Allergy [47]	531	Birth	Dietary and environmental avoidance	Asthma Atopic dermatitis Rhinitis Urticaria	4 years: any allergy (including asthma, atopic dermatitis, rhinitis, and urticaria)
Australian Childhood Asthma Prevention Study [48,49,54]	616	Prenatal	HDM avoidance group Diet (omega-3 acid supplementation) group Combined intervention	Cough, wheeze Asthma Allergic sensitization Total IgE	1.5 years: diet group, wheeze; HDM group, no effect 3 years: diet group, cough; HDM group, sensitization to HDM 5 years: diet group, no effect; HDM group, no effect
Canadian Asthma Primary Prevention Study [50 ^{••} ,55,56]	545	Prenatal	Dietary and environmental avoidance	Allergic sensitization Asthma Allergic rhinitis	HDM levels 1 year: asthma and allergic rhinitis 2 years: asthma 7 years: asthma diagnosis and symptoms

HDM, house dust mite.

^aModified from [57].

asthma rhinitis, atopic dermatitis, and urticaria at age 48 months [47].

The Australian Childhood Asthma Prevention study

The Childhood Asthma Prevention study [48] employed HDM avoidance measures, omega-3 fatty acid supplementation, or both. At 3 years there was a significant reduction of 10% in the prevalence of cough in atopic but not nonatopic children in the omega-3 group and a significant reduction to HDM sensitization in the HDM avoidance group [48]. By age 5 years there was no significance difference between in the prevalence of asthma, wheeze, or atopy in the HDM avoidance or diet groups [49].

The Canadian Primary Prevention of Asthma in Childhood study

A multi-intervention strategy was employed in infants with a positive family history of asthma to reduce exposure to inhaled and ingested allergens and environmental tobacco smoke in the first year of life compared with a control group. Importantly, at 7 years of age there was a 56% reduction in the prevalence of specialist-diagnosed asthma and asthma symptoms compared with the control group. This strategy did not, however, reduce bronchial hyper-responsiveness or allergen sensitization [50**] (Table 1).

Overall, these multi-intervention strategies have shown a significant decrease in asthma symptoms and seem most effective when initiated early in life. The differences have not been consistently demonstrated, however, in objective study outcomes such as lung function or bronchial hyper-responsiveness. Again, long-term follow-up will be needed to see whether these observed differences between treatment groups will be sustained.

Conclusion

The most promising asthma prevention strategies to date have been those that employ a multi-interventional approach combining both diet and environmental manipulations demonstrating a reduction of asthma symptoms. This approach, however, has not resulted in differences between treatment groups in lung function or bronchial hyper-responsiveness. A future area of interest is the use of multiple immunomodulatory interventions such as allergen immunotherapy and anti-IgE that have been associated with reduced allergic sensitization, but have yet to be studied in asthma. More research is clearly needed particularly in the follow-up analysis of multi-intervention trials and to determine the correct age to initiate the intervention, duration, and types of intervention required to prevent asthma. Novel strategies, particularly combination interventions such as immunotherapy with environmental control measures, will need to be explored in the future to determine whether

sustained primary or secondary prevention of childhood asthma is attainable.

References and recommended reading

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 220).

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