Prevention of Asthma in Childhood

a report by

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Should the prevention of asthma be achieved, it will have major implications for public health worldwide. Asthma prevalence has rapidly increased over the last two decades, and cannot be explained simply by genetic change alone. It is most likely caused by a multifactorial process involving complex genetic and environmental interaction. As the majority of people with asthma begin demonstrating signs of the disease within the first six years of life, it is not surprising that efforts to prevent asthma target high-risk young children. This article reviews strategies employed for this aim, including the modification of environmental factors implicated in the pathogenesis of asthma, allergen avoidance, multi-interventional strategies, immunomodulatory interventions, and use of medications.

Environmental interventions are based on the 'hygiene hypothesis': that exposure to certain infections and vaccines early in life may alter the immune system away from a pro-atopic response. Studies of early exposure to animals have shown that exposure to livestock on a farm and/or to pets in the first six years of life has a protective effect against the development of atopy and asthma. However, the association between pet exposure and atopy is not consistent and can be influenced by other factors, such as a maternal history of asthma. Children who attend daycare during the first six months of life or those with older siblings are less likely to have asthma. Use of unpasteurized milk in the first year of life in children living on a farm demonstrated protection against the development of asthma and allergic sensitization. The role of breast-feeding in the development of asthma is not clear. Several studies have shown a protective effect, while others have found an increased risk for asthma in any breast-fed child, or only in those with a maternal history of asthma and a personal history of atopy.

Allergen avoidance was examined in three recent studies involving house dust mite (HDM) avoidance measures starting before birth. A European study of newborns, toddlers, and school-age children with a family history of atopy demonstrated decreased sensitization at age one year, which was lost by age two years in the newborn intervention group compared with the control group. In the toddler and school-age groups, reduction in sensitization was observed at one year of follow-up in the intervention group, but there was no reduction in the occurrence of allergic manifestations. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study found no difference in the development of asthma and atopy at age four years between the groups. At age two years, a small but significant decrease in night-time cough was observed in the intervention group, but was lost by age four years. The Manchester Childhood Asthma and Allergy prevention study showed no difference in mite sensitization, mild wheeze, or cough at age one year between study groups. However, there was a significant reduction in the occurrence of severe wheeze in the intervention group.

Multi-interventional trials including both dietary and allergen avoidance strategies have been used in several studies. Although no differences in lung function or bronchial hyper-responsiveness (BHR) have been demonstrated, multi-interventional strategies, when implemented early in life, have been shown to significantly decrease asthma symptoms. Combined food and HDM allergen avoidance during the first year of life led to a reduction in sensitization and prevalence of asthma up to age eight years in the intervention group compared with the control group, but no difference in lung function or BHR. The intervention group received a combination strategy of decreased exposure to food allergen through exclusive breast-feeding or soya formula, reduced HDM exposure, and avoidance of second-hand smoke. This group experienced less asthma, urticaria, atopic dermatitis, and rhinitis at 48 months. The Australian Childhood Asthma Prevention study employed HDM avoidance or omega 3 fatty acid supplementation used alone or in combination. In atopic children, this study demonstrated a reduction in cough prevalence in the omega 3 group and decreased HDM sensitization in the HDM avoidance group compared with the control group at age three years. At age five years, there were no differences in prevalence of asthma, wheeze, or atopy.
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between the study groups. The Canadian Primary Prevention of Asthma in Childhood study employed strategies to reduce exposure to inhaled and ingested allergens and second-hand smoke during the first year of life in infants with a positive family history of asthma. There was a reduction in the prevalence of asthma and asthma symptoms in the intervention group at age seven years compared with the control group, but no difference in BHR or allergen sensitization. Long-term studies are needed to determine whether the result of these interventions is persistent.

Immunomodulatory strategies have been used in high-risk children to prevent the atopic march and alter the immune system response away from the development of atopy. The effectiveness of the probiotic Lactobacillus GG on the prevention of asthma has not been studied; however, when given to pregnant women with a family history of atopy and then continued as a supplement to infants or breast-feeding mothers, L. GG had a protective effect on the development of atopic dermatitis at age two years compared with placebo. Two open studies found that allergen-specific immunotherapy and sublingual immunotherapy (SLIT) in children with allergic rhinitis (AR) decreased the development of asthma. A recent study demonstrated that monoclonal anti-immunoglobulin E (IgE) used in combination with allergen immunotherapy in children with seasonal AR reduced the AR symptoms by 48% compared with placebo. This is a promising area for future research in asthma prevention, especially in combination with environmental manipulation or medication treatment.

Medications such as inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRAs), and antihistamines have been studied in the secondary prevention of asthma. The rationale of prolonged treatment with daily ICS as a preventive strategy is to decrease both airway inflammation and remodeling, which both lead to BHR and loss of lung function. Therefore, early use of ICS may prevent the development of BHR, decreased lung function, and chronic symptoms characteristic of chronic asthma. It is hoped that this effect will be sustained after discontinuation of the ICS. The first prospective study in young children sponsored Childhood Asthma Research and Education (CARE) network to study this question in pre-school children. This study asked whether daily long-term ICS if given early in life prevents development of asthma in high-risk pre-school children. In this double-blind, placebo-controlled, multicenter study, children two to three years of age with high risk for asthma (positive modified asthma predictive index) were randomized to receive placebo or ICS for two years and then monitored for another year off medications. During the treatment period, the children who received inhaled corticosteroids—fluticasone metered-dose inhaler (MDI) 88mcg twice daily via aero-chamber spacer and face-mask—had significantly more episode-free days (asthma symptoms, medication use, healthcare utilization), less frequent exacerbations, and less supplementary medication use. The beneficial effects were lost during the 12-month observational period after ICS were stopped. The PEAK study demonstrated that while ICS can control active disease, they have little effect on the natural course of asthma after the medications are discontinued, and should not be used for asthma prevention in high-risk pre-school children.

Without an asthma predictive index or biomarker to identify high-risk infants, it is difficult to identify children younger than two years who are at high risk for the development of asthma, as many wheezing infants and toddlers eventually outgrow their symptoms. Indeed, two recent prevention studies that treated infants and toddlers with ICS were unable to demonstrate a difference in asthma burden between treatment groups. One study by Bisgaard and colleagues examined the effect of intermittent ICS given for two weeks during wheezing episodes to infants at high risk for asthma. No significant differences were demonstrated between treatment groups at three years of age in terms of the proportion of symptom-free days and measures of specific airway resistance. Murray et al. studied infants with an atopic parent, looking at the effects of early use of ICS started after the first episode of prolonged wheezing or after two episodes of wheezing. At the age of five years, the prevalence of asthma, use of asthma medications, lung function, and airway reactivity were not significantly different between treatment groups.

Similar to ICS, LTRAs are postulated to decrease mucosal edema, infiltration with eosinophils, bronchial obstruction, and bronchial hyper-responsiveness. This may be particularly important when the symptoms are caused by leukotrienes released during viral infections, particularly respiratory syncytial virus (RSV) bronchiolitis. LTRA, administered within seven days of the beginning of symptoms, were studied by Bisgaard and colleagues in infants hospitalized with RSV bronchiolitis. LTRA used in this setting significantly reduced asthma exacerbation episodes compared with the placebo group for 12 months.

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Antihistamines have also been studied in the prevention of asthma. The rationale behind using cetirizine in asthma prevention is its role in inhibiting allergen-induced eosinophil trafficking into the skin, nose, lungs, and conjuctiva. Thus, its use may decrease airway eosinophil inflammation in children at high risk for asthma. Conversely, loratadine regulates expression of intracellular adhesion molecule type 1 (ICAM-1), a receptor for rhinoviruses, which may have a role in allergen-induced inflammation. It is hypothesized that loratadine can reduce the number of infections early in life, thereby preventing the development of respiratory allergy and bronchial hyper-reactiveness.

In two separate studies, the use of the antihistamines cetirizine and loratadine in high-risk pre-school children showed no effect on the number of pulmonary exacerbations or respiratory infections, no difference in the cumulative asthma prevalence, and no difference once the medications were discontinued compared with placebo. However, in the Early Treatment of Atopic Child (ETAC) study, a post hoc analysis suggested that cetirizine may decrease asthma symptoms by 50% in children with aeroallergen sensitization to HDM or grass pollen. So far, the early use of medication has not resulted in sustained differences in asthma burden or lung function once the medication is stopped. Overall, prevention studies involving asthma medications have not demonstrated sustained improvement in asthma burden.

To date, there is no known strategy that has demonstrated a consistent effect on asthma prevention.