Symposium Cont.
Therapeutic Measures for Prevention of Allergic Rhinitis/Asthma Development

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ABSTRACT
The development of asthma and allergic disease involves not only genetic factors but environmental influences as well. Preventative measures may involve changes in breastfeeding, diet, environmental exposure, medications, and vaccination methods. Breastfeeding is recommended during the first 4–6 months of life. Probiotics should be consumed by mothers during pregnancy and breast-feeding. Solid foods should not be introduced to high-risk infants until four months of age. Consumption of dairy products should be delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age. Exposure to tobacco smoke should be avoided by the expectant mother and by the child after birth. Ample evidence suggests that dust-mite avoidance should be performed. Diets rich in antioxidants and omega-3 fatty acids should be encouraged. No current recommended changes in vaccination practices have been proposed. Because allergy and asthma is a multifactorial process with both complex genetic and environmental components, it is unlikely that a single intervention will have a significant impact on their prevalence. (Allergy and Asthma Proc 25:11–15, 2004)

Over the past quarter-century there has been a significant increase in asthma and allergic disease in the industrialized world. Both asthma and allergic disease have not only a strong heritable component, but are also affected by many environmental factors. These factors may include food and inhalant allergen exposure, exposure to pollutants, and infections with both viral and bacterial agents. Because there has been a rapid increase in asthma prevalence, it would be difficult to say that this is due solely to genetic factors. Therefore, to understand this change in prevalence of asthma and allergic disease, we must evaluate environmental factors that play a role in development of immune responses. Potential approaches in prevention of allergic disease in asthma must consider these factors to be important.

Preventive measures may be primary, secondary, or tertiary. Primary prevention in allergy and asthma may involve avoiding exposure to allergens and irritants. Secondary prevention can involve deterrence of disease expression despite prior IgE sensitization. Methods of tertiary prevention involve reducing morbidity and further worsening for those who already have asthma or allergic disease. Because allergy and asthma is a multifactorial process with both complex genetic and environmental components, it is unlikely that a single intervention will have a significant impact on their prevalence. In this review, proposed measures to prevent asthma and allergic disease development will be discussed and recommendations based upon the literature will be made.

DIETARY MEASURES (Table I)

Maternal Exclusion Diets
Reduced intake of highly allergenic foods in the last trimester has not been shown to prevent allergic disease in high-risk children. Exclusion diets may also
2. Continue breast-feeding for the first year of life or
3. While breast-feeding, avoid peanuts and tree nuts and
1. No maternal dietary restrictions during pregnancy are
4. Solid foods should not be introduced to high-risk
point, due to our lack of ability to measure intrauterine
Breastfeeding
allergen exposure, it is unknown when or if elimination
I
development of eczema during the first two years of life. In that
study, asthma was decreased in the intervention group at
second respiratory symptoms throughout childhood.

**Probiotics**

Probiotics are live microbial food ingredients that are
beneficial to health (e.g., *Lactobacillus*). When admin-
istered to pregnant and lactating mothers, probiotics can
increase the protective potential of breast milk against
development of eczema during the first two years of life.7

Transforming growth factor (TGF)-beta is a key immu-
noregulatory factor in promoting IgA production and indu-
c tion of oral tolerance. During the early postnatal period,
when endogenous TGF-beta production in the intestine is
spare, maternal breast milk constitutes an important exog-
ogenous source.

A Finnish group performed a prospective study in which a
strain of *Lactobacillus* or placebo was given prenatally to
mothers with at least one first-degree relative with atopic
disease.8 The treatment was then continued for six months
in the babies. At two years, the incidence of atopic eczema
in the *Lactobacillus* supplemented group was half of that of
the placebo group (23% vs 46%). Because eczema is the
major atopic manifestation at this age, these findings may
have implications for asthma prevention as well.

**Diet**

What children eat and when they begin eating it may be
important as well in promoting the development of
allergic disease and asthma. Children who eat fresh vege-
tables and oily fish have been found to have a reduced risk
of asthma development.1 Omega 6 fatty acids such as linole-
ic acid, which are low in fish oils, are metabolized to
arachidonic acid and then to prostaglandin E2, which in turn
reduces lymphocyte production of interferon-gamma and
results in up regulation of the Th2 allergic inflammatory
profile. Eicosapentaenoic acid, and omega-3 fatty acid
found in significant amounts in oily fish, competes with
arachidonate acid and inhibits prostaglandin E2 production.

An Australian study showed that children who ate fish
at least once a week (increased omega-3 FA see below) were
30–70% less likely to have asthma than children who ate
fish less often.9 Although one study found that 6 months of
fish oil (omega-3) supplementation did not improve epi-
odic asthma, another study found 9 months of supplemen-
tation did result in a significant FEV1 increase.10

Poor antioxidant intake, which includes vitamin C and
selenium mainly provided by fresh fruit and vegetables,
may be associated with increased bronchial responsiveness
and asthma. A recent study of children in the U.K. found
that children who ate a westernized diet had significantly
more asthma than those who ate an Asian diet, regardless of
race.10 This is consistent with a hypothesis that a diet that is
low in antioxidants and omega-3 fatty acids and high in salt
and omega 6 fatty acids may promote the development of
asthma.

**ENVIRONMENTAL AVOIDANCE**

In the 16th Century, Cordona (an Italian physician) re-
commended that the Archbishop should get rid of his
father’s bedding: a ‘miraculous’ remission of troublesome
symptoms followed. The single largest risk factor for
asthma that has been identified, at least in humid regions, is
sensitization and exposure to house dust-mite allergens.
Avoiding indoor allergens including dust mites, animals,
and cockroach allergens appears to have the greatest potential for benefit in primary, secondary, and tertiary prevention. The risk of asthma can be reduced in half if the levels of house dust-mite allergen exposure are similarly reduced. In a study of house dust-mite-sensitized asthma sufferers in the U.K., in which exposure to other allergens such as pollen and pets was controlled, the level of airway hyperreactivity also doubled for every doubling in the level of house dust-mite allergen exposure. Exposure to house dust mites is widely recognized as an important factor that up regulates allergic sensitization or exacerbates asthma and, as a result, there have been many studies that have tested the efficacy of allergen avoidance. Such studies include those in which asthmatic children have been taken to the Alps or in which allergen levels in beds have been lowered, both of which have achieved improvements in asthma severity. House dust mites thrive in high humidity. Reducing humidity to less than 50% is associated with lower house dust-mite concentrations. Mattress and pillow encasements are effective measures to decrease house dust-mite exposure. Removal of carpeting appears to be the most effective measure to decrease the floor’s house dust-mite concentration. The Isle of Wight study was a prospective randomized study that investigated the efficacy of avoidance of indoor allergens in high-risk infants followed from birth until the age of 4 years. In this study, reduction of house dust-mite levels reduced the prevalence of sensitization and wheezing during the first year of life. Removal of pets from the home is the most effective measure to reduce cat or dog allergen. Unfortunately, this recommendation falls upon deaf ears until disease severity outweighs psychosocial issues and personal attachments. Using HEPA filters and washing animals may be helpful, albeit not as effective as removal.

It is well established that exposure to tobacco smoke in infancy and early childhood is associated with an increased risk for respiratory infections and wheezing, and for sensitization to inhalant allergens. Childhood exposure to tobacco smoke is associated with an increased prevalence of asthma among never smokers, especially in nonatopic subjects. Tobacco smoke has also been shown to increase allergen sensitization and IgE production.

INFECTIOUS AGENTS

Endotoxin is a cell wall product of gram-negative bacteria and has been found to influence many immune processes. It has the ability to: 1) induce T-cell memory to protein antigens, 2) bias T-cells to produce Th1-type cytokines, 3) prevent the development of allergy and asthma before sensitization (but after allergen sensitization has already been established, endotoxin can worsen allergy and asthma severity), and 4) can probably mediate a form of asthma in individuals who are hypersensitive to it. To evaluate a possible connection of endotoxin and asthma, Gereda et al. evaluated the homes of 61 infants with at least three documented episodes of wheezing. Homes of allergen-sensitive infants contained lower concentrations of house-dust endotoxin than those of nonsensitized infants.

Pets in the home have been associated with increased levels of endotoxin. Recent reports have demonstrated that household endotoxin levels were higher in farming households than in nonfarming households. The strongest positive association with household endotoxin levels has been with the number of animals in the home, and a protective association between early exposure to endotoxin and development of atopy has been demonstrated.

The reduction of family size and Western societies may have reduced the extent of microbial exposures. Infectious diseases in early childhood may, in fact, prevent allergic disease. Respiratory viruses may play an important role in the development of asthma. However, the role of both viral and bacterial infections is complicated. Both bacterial and viral infections are important in determining the shift from Th2 to Th1 lymphocyte predominance in infancy. Repeated viral infections other than lower respiratory tract infections early in life may stimulate the immature immune system toward the Th1 phenotype, but thereby reduce the risk for the development of asthma up to school age. Absence of infections in industrialized, well-immunized societies may not allow for this shift to occur and may influence the increase in allergy and asthma.

Bacille Calmette Guerin (BCG) vaccination is felt to elicit a strong Th1 response and potentially decrease the incidence of atopy and asthma. Routine BCG vaccinations have been stopped in western countries where the increase in allergy has been observed. A recent study was performed in Greenland to determine if BCG vaccination would effect the development of atopy. BCG vaccination was given to 1686 children (8–16 years old) and unvaccinated children were used as controls. The risk of atopy was the same in the BCG-vaccinated compared to the unvaccinated.

THERAPEUTIC INTERVENTIONS

Histamine is an important mediator of allergic inflammation. Histamine has been found to trigger virtually all the pathologic responses important in asthma, including vascular dilatation, edema, mucus hypersecretion, and smooth-muscle contraction. Fexofenadine in animal models has been found to prevent the series of Th2 responses that follow allergen sensitization and challenge. Fexofenadine has been found to prevent allergen-induced alterations in pulmonary inflammation and airway function. Cetirizine is being studied for its potential to prevent the atopic march through the airways of atopic infants in a study called “The Early Treatment of the Atopic Child.” Reports have revealed less asthma in the subgroup of atopic infants with grass or dust-mite allergen sensitization. A multicenter NIH/NHLBI-funded study entitled “Prevention of Early Asthma in Kids” was initiated with the goal of enrolling young children with early-onset asthma (2–4 years of age).
and studying the effects of inhaled corticosteroids for two years in a randomized controlled manner. The design incorporates further evaluation to determine whether a course of anti-inflammatory-inhaled corticosteroid therapy can prevent persistent asthma in later childhood. Further studies are needed before antihistamines will be recommended routinely as a preventative measure for allergic disease/asthma development.

Several studies have demonstrated allergen-specific immunotherapy to be effective in preventing progression to asthma in allergic individuals. This supports the view that allergen-specific immunotherapy should be considered earlier in the treatment of rhinitis to prevent progression to a more advanced irreversible type of allergic disease such as asthma. Mastruzzo et al. performed a placebo-controlled, parallel group study of nonasthmatic subjects with seasonal allergic rhinitis. 47% of placebo subjects developed asthma symptoms as opposed to only 14% of those subjects in the allergen-specific immunotherapy group. In a large retrospective survey of nonasthmatic subjects with allergic rhinitis, patients receiving immunotherapy had a 40% less chance of having asthma compared with untreated patients. It is not known exactly why allergen-specific immunotherapy should prevent progression to asthma in some allergic individuals, but one explanation is the potential to attenuate bronchial hyperresponsiveness and lower airway inflammation. Larger studies are needed to define the characteristics of the patients who most benefit from immunotherapy. Measurement of bronchial hyperresponsiveness to inhaled adenosine monophosphate might be a useful way to identify those in whom allergen-specific immunotherapy might be effective in preventing progression to asthma.

CONCLUSIONS

Recommended therapeutic measures to prevent asthma and allergic disease are outlined in Table II. Breast-feeding during the first 4–6 months of life should be encouraged. Exposure of infants to cow’s milk and other highly allergic foods should be delayed as outlined in Table I. Passive exposure to tobacco smoke should be avoided after birth and during pregnancy. Ample evidence supports avoidance of dust mites. Diets high in antioxidants and omega-3 fatty acids should be encouraged. For a variety of sound clinical reasons, breast-feeding for the first 4–6 months of life should continue to be encouraged. Evidence supports giving probiotics to mothers during pregnancy and breast-feeding. Delay of exposure of infants to cow’s milk and other highly allergenic foods also appears to be helpful (Table I). A recent epidemiologic study demonstrates a significant reduction in the risk of childhood asthma if exclusive breast-feeding is continued for at least four months after birth. Avoidance of cow’s milk introduction appears to be more important statistically than the actual duration of breast-feeding. Further studies are necessary to test recommended interventions. The use of scientifically validated avoidance measures is crucial to obtain positive clinical results. We should not advise expensive changes to patient’s homes if they have a minimal effect on allergen avoidance.

REFERENCES

13. Johnson CC and Henley S. Do animals on the farm and in the home reduce the risk of pediatric atopy? Curr Opin Allergy Clinc Immunol 2:133–139, 2002.