PREVENTING vs MANAGING PEDIATRIC ALLERGIES

Clinical and Economic Impact of Nutritional and Environmental Interventions

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NEEDS ASSESSMENT
The prevalence of allergic disease, including asthma; rhinitis; anaphylaxis; drug, food, and insect allergy; atopic dermatitis (AD); and urticaria and angiodoema, has been rising dramatically during the last 2 decades, particularly among children. Among those up to the age of 17 years, the prevalence of food allergies increased from 3.4% in 1997 to 1999 to 5.1% in 2009 to 2011, and the prevalence of skin allergies increased from 7.4% to 12.5%.¹

The economic and emotional burdens of allergic disease are enormous. For AD, for example, the projected third-party payer costs in 1997 to 1998 ranged from $0.9 billion to $3.8 billion when projected across everyone younger than 65 years insured by private insurers and Medicaid. More than one-quarter of all health care costs for patients with AD are attributable to this and comorbid conditions.² Parents of children with AD must deal with sleep disruption and their child’s incessant crying and scratching, as well as ostracism from peers. The family of a child with food allergy must maintain constant vigilance when grocery shopping or eating away from home. These stresses take a toll on quality of life and the child’s self-esteem.³

More than half of children with AD—generally the first clinical manifestation of immunoglobulin E antibody responses—will go on to develop other allergies, usually by their third birthday.⁴ It is therefore essential that pediatric clinicians be aware of the growing problem of pediatric allergy and be able to advise parents about how to avoid initial atopy and the subsequent “allergic march” in their children.⁵ To do so, they must be up to date about the latest research and guidelines with regard to optimal nutritional and environmental strategies. This includes being knowledgeable about the role of breastfeeding and hydrolyzed formula in allergy prevention, the latest findings on diet in pregnancy and lactation, the optimum time to offer infants highly allergenic foods, and the economic impact of primary prevention.

REFERENCES
Preventing vs Managing Pediatric Allergies:
Clinical and Economic Impact of Nutritional and Environmental Interventions

By Alan M. Lake, MD; Mark Boguniewicz, MD; David M. Fleischer, MD

Allergies are among the most common of the many medical conditions that affect children, and they have a huge impact on physical and emotional health and quality of life (QoL).1 The prevalence of allergic disease has risen dramatically throughout the world in recent years, particularly among children.2 In the United States, the most common pediatric allergies are food, skin, and respiratory. According to the US Department of Health and Human Services, the prevalence of food allergies among children up to the age of 17 years increased from 3.4% in 1997-1999 to 5.1% in 2009-2011, and of skin allergies from 7.4% to 12.5%. Though the prevalence of respiratory allergies did not change during this time, they remained the most common type of allergy among children.

Economic burden. Allergic diseases have imposed an increasing economic burden on the US health care system and families with an atopic child. According to a survey of more than 1,600 caregivers of children with a food allergy, the overall economic cost of food allergy is an estimated $24.8 billion annually. This encompasses direct medical costs of $4.3 billion and family costs of $20.5 billion annually, including lost labor productivity and out-of-pocket costs.3 An analysis of 1997-1998 claims data showed that costs of atopic dermatitis (AD) for third-party payers ranged from $0.9 billion to $3.8 billion when projected across all those younger than 65 years who were insured by private insurers and Medicaid.4 Furthermore, the analysis showed that more than one fourth of all health care costs incurred by patients with AD are attributable to AD and comorbid conditions. The costs of asthma also are substantial. From 2002 to 2007, the direct cost of asthma for patients of all ages was $3,259 per person per year, and asthma accounted for 3.68 million missed school days.5

A NEW PATIENT WITH ALLERGY CONCERNS
Mrs. J, who has just moved with her family to a new town, makes her first visit to the new pediatrician for a check-up for her first child. Bryan is a 2-year-old boy who has AD and milk allergy. The AD, which caused Bryan to cry and scratch incessantly, now is controlled with topical treatments, though Bryan occasionally has flare-ups. Mrs. J has learned how to avoid giving Bryan any foods containing cow’s milk protein, which causes him to vomit or break out in hives. Because of the physical and emotional problems Bryan’s allergies have caused, Mrs. J, who is 3 months pregnant, is determined to do whatever she can to prevent her next baby from having allergies.

AD may have the greatest impact on QoL among pediatric allergic conditions. Usually the first manifestation of atopy is asthma. Because of the physical and emotional problems Bryan’s allergies have caused, Mrs. J, who is 3 months pregnant, is determined to do whatever she can to prevent her next baby from having allergies.

Asthma
Food Allergy
Rhinitis
Atopic Dermatitis

WHICH OF THE FOLLOWING STATEMENTS ABOUT ALLERGIC DISEASES IS TRUE?

- Allergic diseases are increasing primarily in developing countries.
- Usually the first manifestation of atopy is asthma.
- Allergic diseases are associated with significant morbidity and cost.
- Sleep disturbances associated with AD stop once AD is in remission.

POLLING QUESTION
patches on the skin, which may appear as raised bumps, leak fluid, and have scratch marks (Figure 1). These patches in infants are likely to appear first on the face and may involve the extensor aspects of the extremities and trunk. The itchiness is worse at night, leading to sleep disturbances. About 86% of surveyed parents of preschoolers with AD reported that during flares their children woke an average of 2.7 times a night—indicating that the parents also lost sleep. Many children with AD continue to awaken at night even when their condition is in remission.

AD and psychological/emotional problems. Children with AD also are at higher risk than their peers of developing psychological disturbances. Preschool children with severe AD were found to exhibit significantly more dependency/clingingness and fearfulness than preschoolers without AD, and more of the mothers of children with AD felt stressed about their parenting. In a comparison of 30 school-aged children with AD with 30 of their peers, children with moderately severe and severe AD (but not mild AD) were twice as likely to develop psychological problems. In a study of almost 3,000 children followed for a decade, even if eczema cleared, AD in infancy significantly increased the risk of conduct problems at the age of 10 years. In children in whom AD persisted beyond the age of 2 years, the risk of conduct problems increased commensurately with the persistence of AD. Perhaps most telling about the distress AD causes, a comparative study of health-related QoL of children with chronic skin diseases (AD, psoriasis, urticaria, or acne) and other chronic conditions (cerebral palsy, renal disease, or cystic fibrosis) showed that only cerebral palsy had a greater impact on QoL than AD.

Food and respiratory allergies. Both of these forms of atopy complicate daily life. A survey of more than 250 parents of food-allergic children using standardized QoL scales showed that families with children with 1 or 2 food allergies had significantly lower scores than previously established norms on 3 of 12 scales—those for general health perception, emotional impact on parents, and limitations on family activities. Dealing with allergies to more than 2 foods had an even greater impact, with those families having scores lower than the norm for 7 scales. Of 87 caregivers who responded to another questionnaire about the impact of their child’s food allergy on family activities, more than 60% reported that food allergy significantly affected meal preparation and 49% said that the condition had an effect on social activities. In addition, 41% reported a significant negative effect on parental stress levels, and 34% indicated that the child’s food allergy impacted school attendance; 10% home schooled their children because of food allergies.

Respiratory allergies negatively impact overall QoL and emotional condition, sleep, social and daily activities, and work or school performance, among other impairments. A survey of the burden of allergic rhinitis in Europe showed that health-related QoL was correlated with disease severity and with the number of days without symptoms during the previous month. Though persistent allergic rhinitis caused the most difficulties, about 82% of those with intermittent disease also reported that their condition caused some impairment in daily life. In a survey of 185 adolescents with asthma, poorer asthma-specific emotional QoL was associated with poorer control of asthma symptoms, missed school, and visits to the clinician for asthma. About 45% of respondents reported feeling depressed, 41% had emergency department visits, and 30% missed school because of asthma.

FIGURE 1. The misery of atopic dermatitis (Click on picture to see video.)
AD is characterized by dry, itchy skin and can involve swelling, “weeping,” and crusting of the lesions. It may cause incessant crying and scratching in infants.

Courtesy of Mark Boguniewicz, MD.
WILL MRS. J’S NEW BABY BE AT HIGH RISK FOR ALLERGIES?

The clinician takes a complete medical history for Mrs. J, her husband, and son Bryan. He learns that Mrs. J has allergic rhinitis and her husband has egg allergy. Because a family history of allergy is the single most important risk factor for developing allergic disease, Bryan’s new pediatrician explores the medical history of the entire family. Since Bryan has allergic disease and both his parents do as well, the as-yet unborn baby is considered at high risk for atopy.

What the studies show. A study in more than 500 infants who were 1 year old showed that compared with children with no family history of allergic disease, those who had 2 or more allergic family members were far more likely to develop food allergy. The increase in risk was more modest in children who had only 1 immediate family member with an allergic disease history.17 Interestingly, in a birth cohort followed for 4 years, sibling atopy was a stronger predictor of clinical disease than atopy in either a mother or father, though being born to an asthmatic mother raised by threefold the risk of having asthma.18 Overall, it is believed that a child without allergic parents may have up to a 20% risk of developing allergy; a child with one allergic parent may have a risk of 40% to 50%; and if both parents are allergic, the child’s risk may be as high as 90%.19

Several large epidemiologic studies have shown that loss-of-function mutations in the gene encoding filaggrin, a major skin barrier protein, increase the risk of AD and other allergic disorders. Patients with these mutations have a leaky epidermal barrier, allowing allergens to penetrate and leading to sensitization and allergic manifestations (Figure 2).20 An analysis of associations between the 2 most common mutations in the filaggrin gene in about 7,000 children found that these mutations are strong genetic determinants of early-onset, severe and persistent AD, as well as early wheezing and asthma, especially in the presence of AD.21 In addition, having a filaggrin mutation is associated with increased risk of allergic sensitization to environmental and food allergens.22

Beyond genetics. Even though genetic factors are highly associated with risk of allergy, practitioners should keep in mind that many children with no family history of atopy also develop allergy and that other factors play a role. One birth-cohort study, for example, showed that formula feeding before 3 months of age was associated with asthma at 4 years of age.18 In an investigation in 20,687 mother-infant pairs, a risk factor for infant AD was a maternal education level of less than 12 years, in addition to parental asthma, AD, and allergic rhinitis.23 Environmental risk factors in the home include fungus on the walls and renovation or painting during pregnancy.

BRYAN AND THE “ALLERGIC MARCH”

In exploring the family’s history, the clinician learns that Bryan, who was delivered vaginally, developed AD when he was 1 month old. The topical corticosteroids prescribed by his previous pediatrician have largely brought the condition under control. Mrs. J breastfed Bryan exclusively for 2 months and then returned to her fulltime job. At that point, Bryan received expressed breast milk along with a supplemental traditional cow’s milk formula (CMF). Within minutes of formula feedings, he often vomited or developed hives. Given Bryan’s new symptoms and his already existing AD, the pediatrician suspected a milk allergy. She switched Bryan to a hydrolyzed formula, and his postprandial symptoms disappeared.

The allergic or atopic march is the sequential development of allergic disease manifestations during early life. Most often the allergic march...
begins with AD and then proceeds to food allergy (as it did with Bryan), followed by rhinitis and asthma (Figure 3). Responses to a questionnaire administered to 2,270 children with AD showed that 71.3% had symptoms of either asthma or allergic rhinitis, with 33.3% reporting symptoms of one condition or the other and 38% reporting symptoms of both. By the age of 3 years, nearly 66% had a least one additional form of atopy.

**How can Mrs. J reduce her new baby’s risk for allergy?**

The clinician asks Mrs. J about her plans for feeding the infant, to help develop a strategy to reduce the new baby’s risk of allergy. Mrs. J responds that she will proceed as she did with Bryan—breastfeed the newborn exclusively for 2 months postpartum and then return to work, relying on expressed milk supplemented by formula. She asks, “While I am pregnant, should I avoid having milk and eggs and other foods that are most likely to cause an allergic reaction in my new baby?” The clinician explains that avoiding these or any foods is not currently recommended, but that she should avoid tobacco smoke and stress (fortunately, neither Mrs. J nor her husband smokes). He then explains why she should aim to have a vaginal birth, as she did with Bryan, because being born by cesarian section (C-section) can increase the risk for food allergy. He commends Mrs. J for planning to primarily provide the baby with breast milk because it has an important role in reducing allergy risk along with its other benefits. With regard to supplemental formula, the pediatrician points out that a hydrolyzed formula also provides protective advantages in patients who cannot be exclusively breastfed for the first 4 to 6 months of life. Lastly, he advises her when and how to introduce complementary foods, including those that are allergenic (Table 1).

**Role of hydrolyzed formula.**

Because Bryan has AD and milk allergy, using a hydrolyzed formula with the next child may reduce the risk of AD compared with standard formulas when used in the first 6 months of life. In hydrolyzed formulas, the milk protein is broken down and is therefore less likely to provoke an allergic reaction. The most compelling evidence for this risk-reducing effect comes from the German Infant Nutrition Intervention (GINI) study, which...
enrolled at birth 2,252 infants at high risk for allergy and has followed them through 10 years. The infants were assigned at birth to 1 of 4 supplemental formulas: CMF, partially hydrolyzed whey formula (pHF-W), extensively hydrolyzed whey formula (eHF-W), and extensively hydrolyzed casein formula (eHF-C). They received the supplemental formulas for the first 4 months, after which time infants generally begin having complementary foods. At the end of a year, the incidence of AD was significantly reduced with the pHF-W and eHF-C formulas, though family history modified the preventive effect of these hydrolysates.\(^{29}\) At the 10-year follow-up, investigators found that the significant preventive effect of pHF-W and eHF-C persisted with regard to AD (no preventive effect was seen on asthma or allergic rhinitis).\(^{30}\) A 2014 meta-analysis of 8 systematic reviews of hydrolyzed formulas studied for the prevention of allergy confirms that in high-risk infants, when exclusive breastfeeding is not possible during the first 4 to 6 months, using hydrolysates may be effective in the prevention of AD.\(^{31}\)

**Maternal diet.** Based on currently available literature and expert opinion, the National Institute of Allergy and Infectious Diseases and the American Academy of Allergy, Asthma & Immunology (AAAAI) do not recommend restricting a woman’s diet during pregnancy or lactation as a strategy for preventing food allergy.\(^{28,32}\) This nonrestrictive approach pertains to all foods, including the most allergenic: cow’s milk, soy, eggs, wheat, peanuts, tree nuts, fish, and shellfish. Data are inconclusive with regard to peanuts, however, for which more research is needed.\(^{28}\)

What to avoid during pregnancy and delivery. Maternal smoking,
which of the following is a risk factor for pediatric allergy?

- breastfeeding for the first 4 to 6 months
- delivery by cesarean section
- maternal ingestion of highly allergenic foods during pregnancy and lactation
- introducing complementary foods between 4 to 6 months of age

stress, and delivery by C-section have all been associated with development of allergy in offspring.

An investigation in 342 children found that at the age of 3 years, children who were exposed prenatally to tobacco smoke had a significantly higher risk than unexposed children of becoming sensitized to food allergens. This effect was less strong when the exposure was only postnatal, but these children were still 2.2 times more likely to undergo sensitization than unexposed children. Other environmental factors related to atopy include exposure to dust mites, molds, animal dander, pollens, ozone and diesel exhaust, and wall fungus. Regarding stress, it appears that intrauterine stress hormone levels, both maternal and fetal, may rise with prenatal maternal stress. This could alter natural immunoregulatory mechanisms and increase the child’s risk for developing inflammatory diseases, including allergy and asthma.

How a baby is delivered affects the immune system of the infant. The infant’s intestine is sterile before birth. With a vaginal birth, the infant acquires bacteria in the mother’s birth canal, and normal maternal intestinal microbiota induce development of the allergic immune system. With delivery via C-section, the newborn misses this opportunity and healthy intestinal flora colonization is delayed for months. Compared with babies born vaginally, those delivered by C-section tend to have higher levels of clostridia, generally considered harmful species, and lower levels of bifidobacteria, which appear to be beneficial. In babies born naturally, this balance is reversed. Bifidobacteria predominate in maternal microbiota, which also include other health-promoting species that colonize the newborn’s intestine. Unsurprisingly, a meta-analysis of 23 studies showed that children delivered by C-section had a 20% increased risk of developing asthma, while another meta-analysis of 26 studies determined that C-section was associated with a moderate risk increase of asthma, allergic rhinitis, and possibly food allergy.

Breast is best. The superiority of human milk over any other form of nutrition for optimum psychological, nutritional, hormonal, and immunologic development of the newborn infant is well established. A meta-analysis showed that compared with conventional formula feeding, exclusive breastfeeding for 3 months reduced the incidence of AD in the first 2 years of life in children with a family history of atopy. Other research has demonstrated an association between early exclusive breastfeeding and protection against early-onset wheezing in the first 4 years of life and cow’s milk allergy in the first 2 years. Based on this and other evidence, the AAAAI recommends exclusive breastfeeding for 4 to 6 months as primary prevention of allergic disease, although it notes some conflicting evidence (Table 2).

Which supplemental formula? In suggesting that Mrs. J use a hydrolyzed formula to supplement breast milk when she returns to work 2 months after her next baby is born, the clinician is following a recommendation of the AAAAI and other professional groups: Infants at high risk for developing allergy who cannot receive breast milk exclusively for at least 4 months should be given breast milk supplemented with a hydrolyzed formula instead of intact CMF for the first 4 to 6 months of life. This recommendation is based on results of the GINI study and is supported by recent research.

One large meta-analysis, while noting inconsistent findings and methodologic shortcomings in some included studies, found limited evidence that prolonged feeding with some hydrolyzed formulas vs. a CMF reduces infant and childhood allergy and infant cow’s milk allergy. A recent analysis of 8 systematic reviews determined that pHF-W and eHF-C formulas—those with documented efficacy based on clinical trials—are appropriate for reducing the risk of AD up to the age of 4 to 6 months in infants 4 to 6 months of age.

TABLE 2. Why the AAAAI recommends exclusive breastfeeding for infants 4 to 6 months of age

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Explanation</th>
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<td>Possibly reduces the incidence of AD in children younger than 2 years</td>
<td>Reduces early onset of wheezing before 4 years of age but not necessarily asthma</td>
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AAAAI=American Academy of Allergy Asthma & Immunology; AD=atopic dermatitis.
high-risk infants who cannot be exclusively breastfed.\textsuperscript{31} An eHF may be slightly more beneficial than a pHF in preventing allergy, but data are inconclusive.\textsuperscript{28} However, eHFs are more expensive than pHFs because they require more processing.\textsuperscript{44} Because soy protein is antigenic like cow’s milk protein and soy formulas have not been proven to reduce allergy risk, soy formulas should not be used to prevent allergies. Amino acid formulas have not been studied for prevention of allergy, so they should not be used.

**Introducing complementary foods.** In the past, medical professionals believed that to lower the risk of allergy, parents should delay first exposure to highly allergenic foods, such as egg, peanut, tree nuts, and fish. Since 2000, however, thinking has shifted in light of observational studies showing that early introduction of allergenic foods may actually prevent food allergy. Therefore, allergenic foods can be introduced between 4 and 6 months of age, as are other complementary foods (Table 3).

For example, in more than 3,700 consecutively born children whose dietary exposures were followed, early introduction of fish and egg, as well as of a variety of grain cereals, decreased the risk of asthma and allergic rhinitis.\textsuperscript{35} In another large study, early introduction of fish decreased the risk of developing AD.\textsuperscript{46} An additional investigation showed that peanut may be less likely to cause allergy when it is introduced early. The prevalence of peanut allergy was 10-fold higher in a group of children in the UK than it was in a similar group of children in Israel, where peanut protein is introduced earlier and is eaten more often and in larger quantities than in the UK.\textsuperscript{47} Such findings have led the AAAAI to determine that currently there is no convincing evidence for delaying introduction of specific highly allergenic foods.\textsuperscript{28}

**PREVENTION MAKES ECONOMIC SENSE**

After reviewing allergy risk-reduction recommendations, the clinician gives Mrs. J a brochure developed by the AAAAI entitled “Preventing Allergies: What You Should Know About Your Baby’s Nutrition” [Click here for PDF], to remind her of what they have discussed. Mrs. J agrees to follow the recommendations the pediatrician has outlined. If the new baby does not develop allergies, the whole family will be happier and will be spared the expense of extra clinician visits, medications, and missed time at work that they have experienced with Bryan.

Although the costs of prevention strategies, such as avoiding tobacco smoke and following infant feeding guidelines, obviously are less costly than the clinician visits and medications associated with allergic disease, it is only recently that the economic impact of primary prevention has been quantified. In one example, a mathematical model incorporating market and GINI study data and expert opinion estimated the savings associated with preventing AD in a high-risk infant by using pHF-W instead of standard CMF to supplement breastfeeding (the cost of the 2 formulas is similar). Researchers determined that this substitution would save $473 per child in direct and indirect health care costs in the first 6 years of life because of a reduction in AD incidence and the condition’s associated costs. The savings that would accrue if all high-risk families used a pHF instead of CMF would be an estimated $352 million, based on an estimated 14-percentage point reduction in the incidence of AD.\textsuperscript{48}

**WRAPPING IT UP**

If nutritional and other interventions can prevent the development of AD, can they stop the allergic march that often follows AD? The answer to this intriguing question remains to be answered. In the meantime, particularly for those with a family history of atopy, the benefits of interventions to prevent allergy in infants are clear: improved physical and mental health for the child, enhanced QoL for the entire family, and reduced costs for family and society.
REFERENCES


1. Which of the following statements about allergic diseases is true?
   A. >50% of children with atopic dermatitis (AD) will proceed to develop asthma and allergies, usually by 3 years of age.
   B. Sleep disruption and mental health problems are associated with infant-onset eczema.
   C. Taking an allergy history, including family history, is important.
   D. All of the above.

2. Which of the following statements is true about the economic impact of allergic diseases?
   A. Third-party payer costs of illness for atopic dermatitis are an estimated $4 million.
   B. Preventing allergic diseases can significantly reduce the personal and national economic costs of treating them.
   C. Indirect costs, such as lost labor productivity, out-of-pocket costs, and lost opportunity costs, have limited impact on overall costs.
   D. Americans spend much less on medical care than on either housing or food.

3. What would you tell a new mother who cannot exclusively breastfeed for 4-6 months?
   A. Current allergy prevention guidelines recommend the use of certain hydrolyzed infant formulas for primary prevention of AD in patients not exclusively breastfed for 4-6 months.
   B. Feeding with the hydrolyzed formulas in the first 4 months has NO preventive effect on cumulative incidence of AD in high-risk children at 10 years.
   C. Exclusive breastfeeding is the only proven way to prevent allergy.
   D. She should not be concerned about allergy risk unless there is a family history of allergy.

4. What would you tell a new mother about complementary foods and allergy risk?
   A. Soy protein may help reduce allergy risk.
   B. She should offer several new food proteins every day.
   C. There is NO advantage to waiting >6 months to introduce complementary foods, including highly allergenic foods.
   D. Waiting >6 months to introduce complementary foods may help avoid allergy risk.

5. What would you tell a pregnant mother about her diet and avoiding allergy risk?
   A. During early pregnancy, she should avoid intake of highly allergenic foods such as peanut, milk, and wheat.
   B. Maternal avoidance of highly allergenic foods such as milk and egg during pregnancy and lactation is not recommended at this time.
   C. In a high-risk family, peanut avoidance during pregnancy or lactation has been proven to decrease risk of allergy.
   D. Higher milk intake during the first trimester is associated with increased asthma.