

# An Integrative Approach to Atopic Disorders in Children

**Lawrence D. Rosen, M.D.**

**A**tophic disorders, including asthma, allergic rhinitis, and eczema, are widely considered to be rising in prevalence at epidemic rates. Support for this concern comes from several multinational sources, including the recently published International Study of Asthma and Allergies in Childhood (ISAAC), which surveyed rates of atopic disease in nearly 200,000 children ages 6–7 in 37 countries and in more than 300,000 children ages 13–14 in 56 countries.<sup>1</sup>

The United States Centers for Disease Control and Prevention estimated that the prevalence of asthma among U.S. children has increased from 3.6 percent in 1980 to 5.8 percent in 2003.<sup>2</sup> Food allergies have also risen in prevalence in the United States, with reactions to peanuts and tree nuts reportedly doubling over a 5-year period.<sup>3</sup> Eosinophilic esophagitis, a formerly rare allergic disorder leading to severe gastroesophageal reflux in newborns, has been rapidly increasing in prevalence in many Western countries, including Australia.<sup>4</sup> Primary care pediatric practitioners are seeing many more infants who have early atopic signs (dermatitis, gastroesophageal reflux, chronic rhinorrhea, and recurrent wheezing).

The atopic march, as it has come to be known, represents the natural tendency of children with early signs of allergic reaction to environmental stimuli (e.g., atopic dermatitis) to progress to more severe manifestations of allergic disease (e.g., asthma).<sup>5</sup> There is already a known strong association between atopic dermatitis and food allergies.<sup>6,7</sup> It is postulated that the classically recognized triad of allergic disorders (eczema, allergic rhinitis, and asthma) will need to be expanded to include other clinical manifestations, including gastrointestinal (GI) and neurodevelopmental symptoms.

Gastroesophageal reflux, inflammation, colic, constipation, lymphonodular hyperplasia, and irritable bowel syndrome have all been linked to atopic disorders, especially food allergies.<sup>8–16</sup> Neurologic and neurodevelopmental conditions, including migraine headaches, Tourette's syndrome, and autism spectrum disorders, have all been associated with an increased prevalence of allergies.<sup>17–21</sup> It is imperative that we consider safe and effective methods not only to treat infants and children with atopic disorders, but to prevent these patients from developing lifelong immune dysregulation and disease.

Why are these diseases increasing so rapidly in prevalence in so many countries? In evaluating likely etiologies for the atopic epidemic, especially environmental factors, integrative practitioners have discovered exciting new possibilities for preventive regimens, suggesting that the tide of the atopic march may be stemmed. Complementary and alternative (CAM) modalities are likely to play a significant role in the prevention and treatment of atopy, and many families are already turning to CAM for children who have eczema and asthma.<sup>22–26</sup>

## The Iceberg Model

As introduced in a review of integrative approaches to autism spectrum disorder,<sup>27</sup> a functional medicine “iceberg” model (Fig. 1) provides a useful tool for understanding a new paradigm of care in children with atopic disorders. The tip of the iceberg represents the visible phenomena in atopic children, including skin rashes, vomiting, runny noses, and coughing. What lies beneath is a genomic predisposition—a familial and individual tendency to develop immune dysregulation under certain environmental circumstances.

While it has long been appreciated that some children are at higher risk for atopic disorders based on family history, it is only now being recognized how complicated the nature–nurture equation might be. Even single-nucleotide polymorphisms (or very small DNA shifts) may not only account for the presence or absence of atopy in a given person, but may also affect the severity of disease, the likelihood of other atopic conditions developing, and the success of various therapies.<sup>28</sup>

What happens next is currently theorized as follows: An individual with a given genomic predisposition, under certain environmental conditions, will suffer metabolomic consequences, manifested by an increase in oxidative stress.<sup>29</sup> At this point, certain immune cells are overstimulated relative to others, resulting in an imbalance between Th1-dominant and Th2-dominant immune responses.<sup>30</sup> There is mounting evidence that even prenatal events (infectious, nutritional, or toxic) may affect Th1/Th2 balance greatly.<sup>31</sup>

Perhaps, practitioners can intervene prenatally, or even pre-conceptually, to prevent the inevitable sequence of events. Th2 dominance leads to an immune dysregulation marked by a heightened allergic response and a proliferation of inflammatory

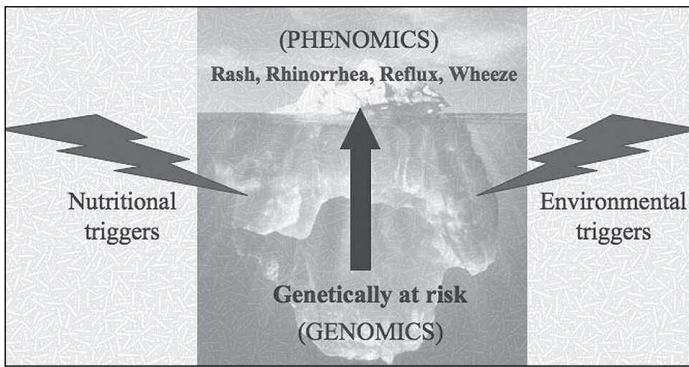


Figure 1. Iceberg model of atopy.

cellular mediators (e.g., cytokines, interleukins, or leukotrienes). Inflammation involves excess mucous production and other clinically observable phenomena recognized as “allergies.”

### Environmental Triggers

Several factors can trigger this immune shift. The “hygiene hypothesis” is the most popular current theory to explain why there is a surge in atopic disease prevalence.<sup>32</sup> According to this theory, many environments are now too “clean”—so humans are not exposed today to as many antigens (bacterial, fungal, or viral) as were previous generations. The reasons proposed for such a change include the eradication of infectious agents by vaccines, anti-infectives (especially antibiotics), and “super-clean” living conditions.

There is some evidence that children raised on farms or exposed to certain livestock may, in fact, develop fewer atopic symptoms.<sup>33</sup> Numerous studies also have supported a correlation between early life antibiotic exposure and atopy (particularly wheezing) in children.<sup>34–37</sup>

With a reduction in infectious exposure, certain individuals may produce altered GI, immunologically active microorganisms, over time, leading to a Th2 immune shift<sup>38</sup> and to subsequent clinical phenomena previously described. Researchers have also examined immunizations as one factor that has changed over time (i.e., newer and more vaccines are given to infants than in the past).

While there is no solid evidence supporting any one vaccine as contributing to the rise in atopy, more literature discusses the role that the mercury-based preservative, thimerosal, may play in the increasing incidence of several connected disorders. Thimerosal, in fact, has been shown to skew immune responses toward Th2 dominance in human nerve cells.<sup>39</sup> Of course, much more research is needed to elicit what role immune-activating agents (such as vaccines) may or may not play but, clearly, thimerosal should be removed from all biologic products unless safety can be ensured.

Other environmental factors have been implicated in triggering allergic responses. These include immune and endocrine disrupting agents in air, water, food, and industrial products.<sup>40–42</sup> It is plausible that the predominant cause of not only the current atopic

epidemic, but also related surges in neurodevelopmental and GI illness diagnoses, is iatrogenic.<sup>43</sup> Understanding the impact that the environment—including but not limited to tobacco smoke—has on the development of atopic disorders will contribute greatly to turning back the tide of these related public-health problems.

One of the most fascinating explanations offered for the increased prevalence in atopic disorders is that another environmental factor—increased societal stress—is shifting the human immune response toward Th2-dominance.<sup>44</sup>

In patients with atopic dermatitis and asthma, psychologic stress has indeed been linked to Th2-shifts correlated with worsening of disease.<sup>45,46</sup> In fact, social support has been shown to strengthen the Th1 immune response to balance Th2 reactivity.<sup>47</sup> These studies support integrating mind–body approaches to treat atopic diseases, via a stress-ameliorating mechanism; this is covered in more detail in the section on CAM therapies.

### Nutritional Factors

Perhaps the factors with the greatest effect on triggering atopic expression are nutritional factors. For patients who are at risk, exposure to certain foods may contribute to severe, lifelong asthma or food allergies. It is important to focus on several areas: maternal pre- and postnatal antigen avoidance; breastfeeding; choice of infant formula supplementation; timing of solid-food introduction; and fatty acid intake (both in breastfeeding mothers and in infants).

However, it is unlikely that one factor is solely responsible for unlocking genomic tendencies toward atopy. For example, contaminants in food and water—not just the proteins in these foods—play a role in allergic-disease expression. What role does the quality of the foods children consume play in atopic disorders? Are parents feeding children whole foods that are rich in anti-inflammatory nutrients (i.e., vitamins, minerals, antioxidants)? If so, it is more likely that the presence and degree of atopy will be altered.

### Pregnancy and Breastfeeding

Advice on what pregnant mothers should or should not eat has varied over time. There is concern that limiting groups of foods—most commonly dairy foods, *Glycine soja* (soy)–based foods, eggs, nuts, wheat, and shellfish—may create nutrient deficiencies (e.g., folic acid, calcium, or iron) that will play a negative role in neonatal development.

General antigen avoidance for the population as a whole is not supported by current data.<sup>48</sup> In families at highest risk (parents and/or siblings with significant atopic histories), avoidance of these most highly allergenic foods, especially peanuts and tree nuts, should be considered during pregnancy and during the breastfeeding period. Maternal lactation diets are covered by the same general guidelines, with one exception: Based on the same data, two international groups advocate different strategies—the American Academy of Pediatrics’ advises avoiding peanuts and tree nuts during lactation, while the European Society for Pedi-

atric Allergology and Clinical Immunology (ESPACI) does not recommend this approach.<sup>49</sup>

If avoidance of food is recommended, patients must be advised about how to ensure proper compensatory intake of vitamins and minerals. Even the choice to breast-feed or not is thought to influence the expression of atopic disease. Both the U.S. and European agencies support breastfeeding as a means to reduce allergic disorders, and this advice seems to be supported by current research studies.

Exclusive breastfeeding for 4–6 months (depending on the study) has been associated with a lower risk of developing atopic dermatitis, food allergy, allergic rhinitis, and asthma.<sup>50–53</sup>

### Essential Fatty Acids

More-recent studies have examined the role of essential fatty acids (EFAs) in reducing allergic disease. The evidence is very good for prenatal prevention of atopy when mothers ingest higher amounts of omega-3 polyunsaturated fatty acids (PUFAs).<sup>54</sup> It also appears that babies who ingest breast milk relatively richer in omega-3 fatty acid are less likely to develop allergic symptoms.<sup>55,56</sup> This effect is most prominent in babies who are at highest risk genetically.

Interestingly, the results of feeding infants PUFAs directly are not as clear. Some studies of dietary modification with omega-3 PUFAs in children at high risk demonstrated reduction in atopy,<sup>57,58</sup> and another study showed improvement with a supplement of *Oenothera biennis* (evening primrose) oil, an omega-6 PUFA.<sup>59</sup> Perhaps it is the balance of the two EFAs that is most important, and one must also take into account preexisting dietary deficiencies and genomic factors. More research is clearly needed in this realm before universal recommendations can be made.

### Formula Feeding

If exclusive breastfeeding is not possible, U.S. and European experts are in agreement regarding the use of soy formulas for atopic prevention in high-risk infants—these experts are solidly opposed to soy formulas.<sup>49</sup> The authors of a Cochrane Database Systematic Review (SR) concur.<sup>60</sup> What these experts recommend for these high-risk babies (again supported by another Cochrane SR)<sup>61</sup> are hydrolyzed protein formulas.<sup>49</sup> These formulas may contain extensively or partially hydrolyzed cow's milk proteins (casein or whey), and there is debate about whether these formulas are both equivalently effective for preventing atopic expression.<sup>62</sup> Most experts currently recommend extensively hydrolyzed products, but cost (more than standard formulas) and availability (less available than standard formulas) often influence whether or not such products will be used.

Some children will experience such severe atopic symptoms, even on these formulas, that these children may need

elemental amino-acid formulas. Although such formulas are often digestively well-tolerated compared with cow's milk, it is generally advisable to avoid recommending products with

other animal milks (goat, sheep) for infants at high risk for atopic disease.

Another issue concerns the increasing numbers of infants, with no contributory family histories, presenting with eczema, rhinorrhea, reflux, and wheezing. The consensus on treating atopic disease in these infants seems to point toward

exclusive breastfeeding with maternal antigen avoidance, or, if this is not possible, using extensively hydrolyzed formulas.

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### Solid-Food Introduction

There continues to be much debate about the optimal time to introduce solid foods to infants—for both those in the general population and those at high risk. With increasing prevalence of allergic disorders, some experts are advocating for delayed solid-food introduction in all babies until 6 months, with the introduction of highly allergenic foods as follows: dairy products at 12 months; eggs at 24 months; and peanuts, tree nuts, and shellfish at least after 36 months.

The American College of Allergy, Asthma and Immunology judiciously concluded in its published consensus document: "Pediatricians and allergists should cautiously individualize the introduction of solids into the infants' diet."<sup>63</sup> These guidelines are also recommended by major U.S. and European groups, but only for infants at high risk.<sup>49</sup>

Early solid feeding (prior to 4 months of age), particularly of gluten-containing products, does seem to be associated with atopic disease as well as with celiac disease.<sup>64,65</sup> Some experts have postulated a similarly negative role for gluten with respect to increased risk for other autoimmune and neurodevelopmental disorders. There have also been several studies exploring treatment of atopic disorders, particularly eczema<sup>66,67</sup> and asthma,<sup>68,69</sup> with various nutritional interventions.

Avoiding specific food allergens and encouraging the consumption of particular nutrients (e.g., magnesium, zinc, PUFAs) does seem to benefit a significant subset of children at risk for atopic disorders.

### Complementary and Alternative Medical (CAM) Therapies

There are many CAM therapies that are reportedly effective for preventing and treating allergic disorders. Natural therapies for allergies and related conditions, as reviewed in the Natural Medicines Comprehensive Database<sup>70</sup> and the Natural Standard,<sup>71</sup> number well over 100. Many of these are botanical products, some of which are covered below.

Some CAM therapies, such as energy healing (e.g., Reiki), lack published data to support widespread use, but are generally con-

sidered to be safe and may be particularly helpful for addressing conditions, such as asthma, with a large stress component. Other widely used modalities have more of an evidence base to consider, including Traditional Chinese Medicine, mind–body therapies, manual therapies, and homeopathy. These therapies, along with selected biologically based remedies, are discussed in more detail below.

### Probiotics

Probiotics have long been known to play a role in immunomodulation.<sup>72</sup> It is precisely this role that suggests that probiotic supplementation and support can be used for atopy prevention and treatment.<sup>73,74</sup> Several fascinating studies have, in fact, demonstrated that probiotics—given prenatally to women and then postnatally to either breastfeeding mothers or directly to formula-fed infants—can reduce the incidence of atopic dermatitis by half in infants at high risk.<sup>75,76</sup> These effects, noted in randomized, controlled trials of *Lactobacillus* GG, have held up to 4 years postnatally.

Prebiotics, special oligosaccharides that act as nutrients for probiotic growth, have also been shown to prevent eczema in a vulnerable infant population.<sup>77</sup> Treatment studies have been generally encouraging as well.

One study demonstrated a significant airway anti-inflammatory effect of lactic-acid bacteria, supporting the idea that probiotics can suppress allergy-induced inflammation.<sup>78</sup> This study has remarkable implications for asthma treatment.

Several randomized controlled trials have pointed toward a positive effect of probiotics and prebiotics on the course of atopic dermatitis.<sup>79–82</sup> One trial found no such effect.<sup>83</sup> It is likely that it will be necessary to elucidate more clearly which strains and doses of probiotics and prebiotics have the greatest effects for specific atopic conditions.

### Botanicals

Hundreds of botanically derived products have been used for millennia to treat eczema, allergic rhinitis, and asthma. Some of the most commonly prescribed conventional medications are derived from natural products, including one of human biology's most potent anti-inflammatory—steroids. Because of the wide use of these biologically active remedies, it behooves practitioners to familiarize themselves with what their patients and their families are using.

There is great potential for both help and harm with any biologically based therapy. Careful, judicious, individualized, and evidence-guided integration of conventional and CAM therapies may prove to be the most safe and effective treatment for atopic disorders.

Aromatherapy, the use of inhaled essential oils derived from herbal sources, is also used by individuals with atopy, particularly to reduce stress and inflammation. There are, however, very

few botanicals that have been formally studied in children. It is important to remember that many traditional herbalists believe in the healing power of whole plants and that the current pharmaceutical practice of distilling plants down to one active ingredient may not offer us the same efficacy or safety.

In any case, one of the most promising herbals for allergy treatment is *Petasites hybridus* (butterbur). According to the Natural Medicine's Comprehensive Database,

[t]he active constituents of butterbur are the sesquiterpene compounds, petasin, and isopetasin. Butterbur extracts also contain volatile oils, flavonoids, tannins, and pyrrolizidine alkaloids. . . . In allergic rhinitis, butterbur and purified petasin decrease blood concentrations of histamine and leukotrienes. They also appear to decrease priming of mast cells in response to contact with allergens.<sup>70</sup>

A specific butterbur leaf extract (Ze 339) has been shown to relieve allergic rhinitis effectively and safely.<sup>84</sup> The same product, interestingly, has been effective for preventing migraine

headaches in children and adolescents<sup>85</sup>; perhaps it is the Th-2 dominant link between the conditions discussed earlier that explains these findings.

Two other botanical products—*Boswellia serrata* (boswellia) gum resin and *Pinus maritimus* (French maritime pine bark; Pycnogenol®

Horphag Research, Ltd., St. Peter Port, Gurnsey, Channel Islands, United Kingdom)—have been shown to reduce asthma symptoms.<sup>86–87</sup> Given most families' concerns about long-term steroid treatment, it would make sense to look carefully at these and other promising therapies as adjuncts in the integrative treatment of asthma and other atopic disorders.

### Traditional Chinese Medicine

In Traditional Chinese Medicine (TCM), acupuncture, in particular, has been singled out as a therapy with great promise for use to address such conditions as asthma. TCM considers acustimulation one potential part of the care of children with atopic conditions. Botanical remedies, nutritional modulation, *tui na* (massage), *gua sha* (scraping), cupping, and mind–body therapies are also incorporated. Kielczynksa's case description of Traditional East-Asian Medicine used to treat a child with asthma<sup>88</sup> provides an idea of the holistic nature of the TCM approach to atopy. There have been promising trials of TCM for allergic rhinitis<sup>89–91</sup> and a Cochrane Database SR of Chinese herbal medicine for eczema.<sup>92</sup>

### Mind–Body Therapies

Among the most popular, widely studied, safe, and effective treatments for the stress component of atopic disorders are mind–body therapies. Any therapy—including self-hypnosis, guided imagery, biofeedback, Mindfulness-Based Stress Reduction, and

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meditation—that acts to reduce immune hyperstimulation via psychoneuroimmune pathways<sup>93</sup> and that teaches self-care and control has the potential to be quite effective. This has been demonstrated in children with asthmatic dyspnea<sup>94</sup> and children with severe eczema.<sup>95</sup> Yoga, with its blend of breathwork, relaxation training, and movement, is quite well-matched for children and adolescents with asthma.<sup>96</sup>

### Manual Therapies

Manual therapies include, but are not limited to, chiropractic, osteopathic manipulation, and therapeutic massage. Various theories abound regarding the mechanism for manual treatment of atopic disorders, most commonly for asthma. Some researchers posit that there is an anatomical effect on respiratory musculoskeletal function, while others regard these therapies as a method of rebalancing sympathetic and parasympathetic neurologic tone.

The reviewers of a large Cochrane Database SR concluded, not surprisingly, that more research is needed in all areas<sup>97</sup>; these therapies are not comparable to each other and deserve specific trials for each and every one. Despite the publicity surrounding the negative findings of a *New England Journal of Medicine* paper on chiropractic treatment for childhood asthma,<sup>98</sup> this modality continues to be perhaps the most widely utilized CAM treatment in children for all atopic disorders. Therapeutic massage trials for asthma and atopic dermatitis have been published, both with positive results.<sup>99,100</sup> Osteopathic manipulative therapy has been studied also, with one randomized trial demonstrating a positive effect in asthma treatment.<sup>101</sup>

### Homeopathy

Shalts has covered the rich history of homeopathic treatment of allergic disorders, noting that “homeopaths pioneered both the research and treatment of allergies.”<sup>102</sup> There are as many homeopathic treatment regimens for children with allergies as there are children with these conditions. One of the beauties and challenges of classical homeopathic therapy for atopy is that one must individualize the remedy for each child’s constitution and presentation.

When homeopathy works (despite the difficulty of explaining the mechanism in conventional medical terms), it works quickly and safely for a long period of time. Conducting studies of homeopathy is difficult, but the authors of one published trial found homeopathy to be significantly superior to placebo for treatment of allergic rhinitis,<sup>103</sup> and the author of a case series found an 87.6 percent success rate for treatment of respiratory allergies.<sup>104</sup>

### Conclusions

Clearly, given that there is an epidemic of allergy-related disorders, the challenge to medicine is *not* to develop more aggressive and costly treatments but to devise and implement more effective prevention strategies. Integrative medicine and, in particular, integrative pediatric practitioners, are well-positioned to advocate for such a paradigm shift.

Holistic integration of CAM and conventional strategies coupled with dedication to evaluating and alleviating environmental triggers can help families avoid the allergic march to life-long atopic disorder. This integrative approach is well-represented by the results of the Canadian Childhood Asthma Primary Prevention Study.<sup>105</sup> This study has already proven that a balanced, integrative approach can yield dividends. Following nearly 500 children over 7 years, the researchers have demonstrated that avoidance of house dust, pets, and environmental tobacco smoke along with encouragement of breast-feeding and delayed introduction of solid foods significantly reduced allergic disease.<sup>105</sup>

While it is important to demonstrate safety and efficacy of specific therapies, it is often the practical combination of several approaches (e.g., nutritional modification, environmental trigger avoidance, or stress-coping skill training) that make the most sense and the biggest difference. □

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**Lawrence D. Rosen, M.D.**, is chair of the Integrative Pediatrics Council and is in private practice, in Old Tappan, New Jersey.

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