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Atopic Dermatitis and Asthma: Parallels in the Evolution of Treatment

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ABSTRACT. *Objectives.* To review epidemiologic correlations between asthma and atopic dermatitis (AD), identify common features in disease pathophysiology, and review steps involved in the development of asthma therapy guidelines to assess the appropriateness of a similar process and approach for AD.

Methods. A 7-member panel representing specialists in dermatology, allergy, asthma, immunology, and pediatrics from around the United States convened to review the current literature and evolving data on AD. Participants presented reviews to the panel on the epidemiology of asthma and AD, the genetic predisposition to allergic disease, the current understanding of the immunopathophysiology of AD, interrelationships between the pathologic pathways of asthma and AD, evolving treatment concepts and options in AD, and the applicability of the asthma treatment model and how it may be adapted for guideline development for AD. Commentary and criticism were recorded for use in document preparation.

Results. There are clear epidemiologic parallels in asthma and AD. Importantly, AD frequently is the first manifestation of an atopic diathesis, which occurs in genetically predisposed individuals and also includes asthma and allergic rhinitis. Up to 80% of children with AD will eventually develop allergic rhinitis or asthma later in childhood. This classic "atopic triad" has numerous pathophysiologic elements in common, including cyclic nucleotide regulatory abnormalities, immune cell alterations, and inflammatory mediators and allergic triggers. New therapeutic options that target underlying immune mechanisms are available, and their place among treatments for AD is becoming established. Guidelines of care have been developed for asthma. The panel noted that the National Institutes of Health/National Heart, Lung, and Blood Institute guidelines for diagnosis and management of asthma, first issued in 1991, had a tremendous positive impact on many aspects of asthma treatment. It not only created a heightened awareness that asthma is a disease of chronic inflammation, but it also provided unified approaches for therapy and opened new areas of basic science and clinical research. In addition, the guidelines spurred interactions among

physicians of various specialties and stimulated a great quantity of research in asthma therapy. It is anticipated that AD therapy guidelines would have similar positive outcomes.

Conclusions. The panel concluded that, on the basis of current information and evolving therapeutic options, a clear rationale exists to support AD guideline development. The many parallels between AD and asthma suggest that processes and approaches used for the asthma therapy guidelines would be appropriate for AD. *Pediatrics* 2003;111:608–616; *allergy, asthma, atopic dermatitis, treatment guidelines.*

ABBREVIATIONS. AD, atopic dermatitis; IgE, immunoglobulin E; NHLBI, National Heart, Lung, and Blood Institute.

Epidemiologic studies conducted during the past 2 to 3 decades indicate that the prevalence of atopic diseases has risen in Western and developing countries.^{1–5} Conservative estimates state that lifetime prevalence of atopic dermatitis (AD) in young schoolchildren in both Western Europe and the United States is now in the range of 10% to 20%.^{6,7} In the United States, the overall age-adjusted prevalence of asthma rose from 30.7 per 1000 in 1980 to 53.8 per 1000 in 1993–1994.⁸ The increase in atopic diseases has been so dramatic that it is widely recognized that we are in the midst of an allergy pandemic. Although much recent attention has focused on the rising rate of asthma, it is important to note that rates of AD, allergic rhinitis, and other atopic diseases have risen similarly.^{5,8} The evidence that asthma and AD are increasing and that AD is a risk factor for childhood asthma occurrence, severity, and persistence are reviewed below.

The prevalence of asthma is rising. Epidemiologic surveys in Western countries have assessed the change in prevalence of asthma, mainly among children. Most of these studies have concluded that a significant increase in asthma has occurred in the last decades.⁵ In the United States, the overall age-adjusted prevalence of asthma increased 75% between the early 1980s and 1994. The prevalence among children ages 5 to 14 increased 74%. In 1980, the total estimated number of people with self-reported asthma was 6.8 million. By 1993–1994, that number had grown to 13.7 million.⁹ Among children up to 4 years of age, the prevalence increased 160% (Fig 1).⁸ In 1998, the estimated number of people in the United States with asthma had risen to 17 million.¹⁰

The prevalence of AD has risen along with increased asthma prevalence. Numerous epidemio-

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Rate per 1,000 Population*

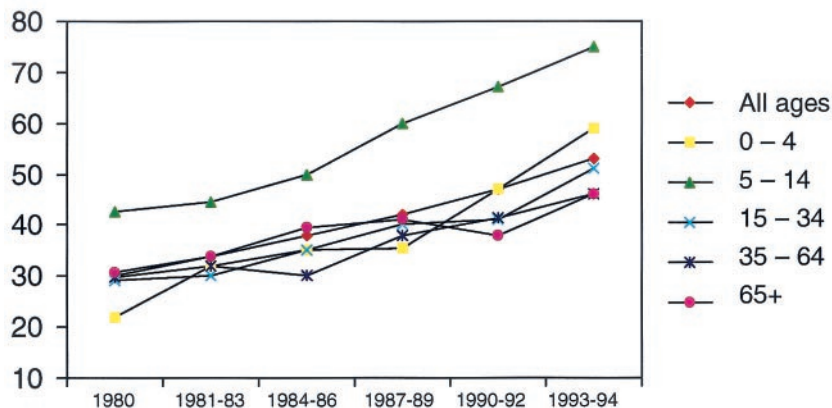


Fig 1. Trends in asthma prevalence by age, age-adjusted for the 1970 US population.⁸

logic studies have demonstrated clear increases in the prevalence of AD.¹¹ For example, a study of Oregon schoolchildren found a history of AD reported for 17.2% of the children, a figure that is comparable to the 15.6% prevalence demonstrated in northern European countries.^{1,6,12} Another recent study of 5- to 9-year-old Japanese schoolchildren assessed that there was evidence of AD in 21% of the children.¹³ A cohort study in Britain found the prevalence of AD in children to be 5.1% in those born in 1946, 7.3% in those born in 1958, and 12.2% in those born in 1970. In 1994, 20% of children 3 to 11 years of age were reported to have AD (Fig 2).^{14,15} Overall, AD has increased 2- to 3-fold during the past 30 years and currently is believed to affect between 10% and 15% of the population at some point during childhood.^{16,17}

CORRELATION OF AD AND ASTHMA

AD predates the development of asthma and allergic rhinitis, suggesting that AD is an "entry point" for subsequent allergic disease.¹⁸ In a study that examined the relationship between AD in infancy, sensitization to aeroallergens, and presence of allergic airway disease, 69% of infants who had AD in the

first 3 months of life were sensitized against aeroallergens by 5 years of age. The rate of aeroallergen sensitization increased to 77% of children when both parents had a positive history for atopic disease.¹⁹ By 5 years of age, 50% of children with early AD and a strong family history of allergy had allergic airway disease.¹⁹ Indeed, up to 80% of children with AD will develop allergic airway disease at some point in childhood.²⁰ In 40% to 50% of children, this allergic airway disease manifests as asthma.¹¹ It is frequently observed that some patients "outgrow" their AD as respiratory allergy develops. Nevertheless, it is estimated that 15% to 30% of patients with AD have coexistent asthma.²⁰

Children with coexistent AD frequently have more severe asthma than children who have asthma and do not have AD. A study by Buffum and Setticone²¹ identified a link between the presence of AD and prognosis of asthma in childhood. A 10-year evaluation of asthma patients without AD indicated that 41% were well, 52% had mild asthma, and 5% had severe asthma. In contrast, among asthma patients with AD, 34% were well, 54% had mild asthma, and 11% had severe asthma or had died of the disease. In addition, the severity of AD seems to be directly

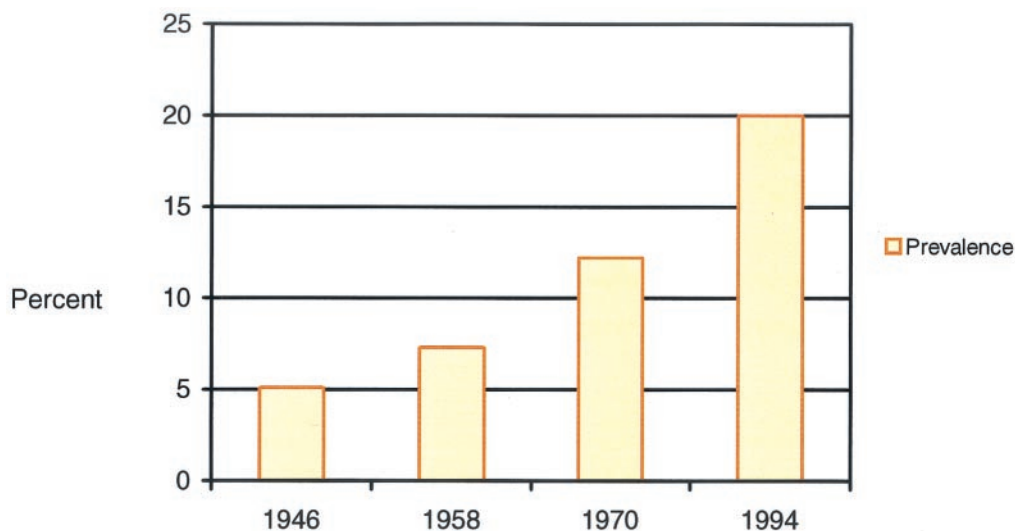


Fig 2. Trends in AD prevalence among British children.^{14,15}

correlated with the severity of the asthmatic response. Brinkman et al²² compared bronchial effects of allergen challenge in patients who had concomitant AD and asthma with a range of disease severities. Patients with coexisting severe AD and mild asthma developed the most pronounced late asthmatic responses after allergen challenge, leading the authors to suggest that disease mechanisms that are activated in AD may predispose patients to airway inflammation. Finally, it has been suggested that the allergen sensitization that occurs via the skin in patients with AD also evokes a strong systemic allergic response, characterized by elevations in serum immunoglobulin E (IgE) antibodies, eosinophils, macrophages, and T cells. These biological markers of leukocyte activation have been shown to correlate with the severity of AD and also may play a role in respiratory allergy in genetically predisposed individuals.¹⁸

In summary, the evidence is strong that AD is a risk factor for childhood asthma occurrence, severity, and persistence. The mechanisms by which AD influences the course of asthma are likely related to early IgE production and consequent allergen/IgE reactivity.^{11,15,18,19,22} The pathophysiologic elements that link these disorders are discussed further in "Common Pathophysiologic Mechanisms in AD and Asthma."

ENVIRONMENTAL AND LIFESTYLE FACTORS IN THE ALLERGY PANDEMIC

The causes of the pandemic remain unknown. Although it is certain that a family history of allergic disease is a strong predisposing factor for AD, genetic factors alone cannot explain the rapid increase in prevalence that has occurred within a relatively short period. Instead, researchers have pointed to certain epidemiologic observations that suggest a Western lifestyle, urbanization, and development have important roles in the increasing prevalence of atopic diseases (Table 1).¹² Among the consequences of Westernization have been profound changes in environmental factors. Increased exposures to allergens and outdoor and indoor pollution are implicated factors. In addition, the profound societal changes related to Westernization have led researchers to propose a role for lifestyle factors, such as changes in diet, body weight, antibiotic use, and stress.^{12,23,24} For example, 1 theory points to an in-

TABLE 1. Epidemiologic Observations That Suggest a Role for a Western Lifestyle, Urbanization, and Development in the Increasing Prevalence of Atopic Diseases¹²

Increasing prevalence during the past 30 y in industrialized Western countries
Prevalence higher in immigrants to Western countries than in native lands
Prevalence higher in industrialized countries with a market economy
Prevalence higher in urban than in rural areas
Prevalence higher in privileged socioeconomic groups and smaller families
Increase most obvious in children and young adults
Increasing prevalence with increasing industrialization in developing countries

crease in the prevalence of allergic diseases as a result of the reduction of early childhood infectious diseases through vaccinations and increased use of antibiotics. According to what is known as the "hygiene hypothesis," infections with viruses influence the developing immune system, generating an immune response that would be less likely to be partial to allergen sensitization in childhood. However, decreasing the frequency of infections through vaccinations would prevent the maturation of the immune system and increase the risk of developing atopic diseases.²⁵ In contrast to the impacts of Westernization, a recent survey of parents in rural areas of Austria, Germany, and Switzerland found that exposure of children younger than 1 year, compared with those 1 to 5 years of age to stables and consumption of farm milk was linked to lower frequencies of IgE reactivity (12% vs 29%), asthma (1% vs 11%), and hay fever (3% vs 13%). Moreover, continual exposure to stables until 5 years of age was associated with the lowest frequencies of AD, asthma, and hay fever.²⁶ Although many interesting associations between various factors and atopic diseases have been noted, the relative impact of any individual factor is difficult to determine. Carefully designed epidemiologic studies are needed to discern the real cause-and-effect relationships.¹²

GENETIC FACTORS IN ASTHMA AND AD

Although changing environmental and lifestyle factors are likely to be responsible for the recent rise in the prevalence of atopic diseases, it is clear that interactions between genes and environment both contribute to the genesis of atopy.^{27,28} Genetic studies, using the modern techniques of molecular biology, are expected to advance our understanding of atopic diseases and refine our approaches to its management. They may provide improved definitions of disease, identify subgroups of disease, and reveal new targets for treatment. In addition, if genetic studies can identify individuals who are at risk for atopic diseases, then rational strategies for disease prevention potentially can be developed.²⁸

A number of genetic linkages using genome-wide searches have been performed for asthma and AD. For asthma, 7 linkage studies have been conducted. These have identified regions of genetic linkage on chromosomes 2, 4, 5, 6, 7, 11, 12, 13, and 16 (Fig 3).²⁸ A number of these contain genes involved in immune function, including those that encode various interleukins, major histocompatibility complex proteins, and a component for the high-affinity IgE receptor.²⁸ In addition, genome-wide screens for other immune disorders, such as irritable bowel syndrome, indicate a coincidence with asthma linkages.²⁸

Two genome screens for AD have been reported. The first has identified linkage of AD to chromosome 3q21.²⁹ The second screen found linkage of AD to chromosomes 1q21, 17q25, and 20p.²⁸ None of these regions coincides with loci that previously have been identified for asthma and atopy. However, more focused linkage studies have identified some common chromosomal linkages between AD and asthma (5q31–33, 11q13, and 13q 12–14).^{30,31} It is interesting

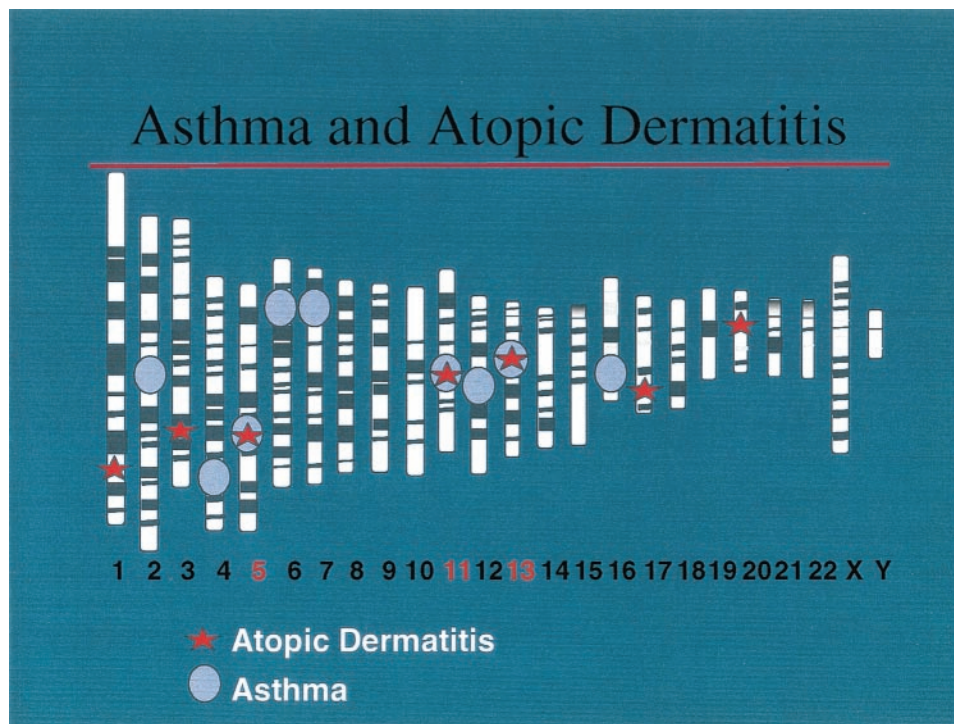


Fig 3. Coincidence of asthma and AD linkages.

to note that 3 of the AD linkages do correspond with known asthma loci, indicating that AD shares genetic determinants with asthma (Fig 3).

COMMON PATHOPHYSIOLOGIC MECHANISMS IN AD AND ASTHMA

Epidemiologic findings suggest that the burden of AD and asthma to individuals and society will rise. Fortunately, a great deal of progress has been made in our understanding of key processes that underlie atopy. As might be expected, parallels and interrelationships demonstrated in epidemiologic studies of AD and asthma are mirrored in common pathophysiologic mechanisms. Differences in clinical and histopathologic manifestations may lie more in the differences between the skin and lung themselves—their distinct microenvironments, resident cells, types of environmental exposures, and unique, specialized immune responses—than in underlying mechanisms.²⁰ A brief overview of common pathophysiologic elements is provided below.

Pathogenic Mechanisms Are Central to Both AD and Asthma

AD and asthma both can be characterized as manifestations of an exaggerated inflammatory response to environmental triggers, including irritants and allergens. This is accompanied by increased production of IgE and eosinophilia.^{20,32} An additional key element is the development and activation of T_{H2} cells, a subset of T helper cells that initiate and maintain local tissue inflammation.²⁰ Interleukin (IL)-4 synthesis by T_{H2} cells stimulates production of IgE, and IL-5 synthesis by T_{H2} cells drives bone marrow differentiation of eosinophils.^{18,32} In addition, increases in phosphodiesterase activity in atopic mono-

cytes can cause Th_2 skewing, and phosphodiesterase inhibitors may reverse immune and inflammatory abnormalities.³³ Some children and adults with AD may not demonstrate specific IgE sensitization to common allergens and may represent a subset of patients with distinct pathogenetic features.^{34–36}

It is uncertain whether these individuals have consistently distinct differences in clinical phenotype or course of atopic disease. Although a detailed comparison of the features of AD and asthma is well beyond the scope of this article, commonalities and dissimilarities are presented in Table 2.³⁷

Epicutaneous Allergen Sensitization Evokes a Systemic Allergic Response

Because AD often predates respiratory allergy and predisposes patients to more severe asthma, it is believed that epicutaneous allergen sensitization may evoke a systemic allergic response that crucially impacts the development and course of asthma later in childhood. Although the inflammatory process in AD is localized to the skin, IgE, eosinophils, and T_{H2} cells can circulate throughout the body; eosinophils and T_{H2} cells have a specific capacity to traffic to sites of inflammation.¹⁸ Evidence that allergic sensitization through the skin can directly affect T_{H2} -mediated responses and airway reactivity has been demonstrated in an animal model.³⁸ Spergel et al³⁸ demonstrated that epicutaneous sensitization to the protein allergen ovalbumin on tape-stripped skin induced a dermatitis in mice that might provide an animal model of AD and amplified IgE production. In that system, as well as a subsequent study by Herrick et al,³⁹ epicutaneous sensitization, followed by aerosolized ovalbumin, led to reactive airways and inflammatory features of asthma. These data

TABLE 2. Features, Factors, and Immune Mechanisms in AD Versus Asthma

	AD (With IgE reactivity)	Asthma (With IgE Reactivity)
Total IgE level	↑ ↑ IgE	↑ IgE
Allergens	Multiple allergens • Food • Aeroallergens • Microbes	Aeroallergens
Viral infections	Yes	Yes
Autoantigens	Yes	No
Superantigens	Yes	No
Onset	Usually predates asthma	Later onset
Breastfeeding	Prophylactic effect	Prophylactic effect
Adhesion molecule expression	More prolonged E selectin ↓ vascular cell adhesion molecule endothelial expression	
Epithelial barrier dysfunction	Primary defect (↓ ceramide)	Secondary defect (postinflammation)
Eosinophils	More degranulation in lesions ↓ ↓ apoptosis	Less degranulation ↓ apoptosis
Genetics	Familial + maternal	Familial + maternal
Route of entry of allergens	Gastrointestinal, airways, skin	Airways
Nonallergic triggers	Yes	Yes

supply direct evidence that stimulation of skin inflammatory responses has systemic consequences and suggests that AD can lead to the development of asthma.

Allergic Triggers as a Subset in AD

As discussed above, AD is characterized by elevated levels of serum IgE and sensitization to environmental allergens, including foods, indoor inhalants, and outdoor inhalants.²⁰ It is interesting to note a relationship between the atopic march, which is the progression from initial AD to later development of respiratory allergy, and the types of and changes in allergic sensitization that occur during childhood. Epidemiologic studies have shown a progression of atopic sensitization from food allergens to inhalant allergens.⁴⁰ The German multicenter atopy study, which prospectively followed 1314 infants for >10 years, demonstrated that approximately 10% of infants were sensitized to food allergens at 1 year of age; however, allergic reactions to food were seen in 8% of children. By age 6, only 3% of children were sensitized to food allergens. Conversely, 1.5% of infants were sensitized to inhalant allergens at 1 year; at 5 years, 30% of children were sensitized to inhalant allergens.^{19,40} This study also demonstrated that the combination of AD, atopic family history, and food sensitivity is highly predictive of future respiratory allergy and asthma.¹⁹

Although the incidence of food allergy in an “unselected” population of patients with AD is uncertain, studies have estimated that one third of children with AD have coexisting food allergy, which is most common among children with moderate to severe AD.⁴¹ Exposure to foods may or may not induce eczematous dermatitis in these children, whereas other nondermatitis symptoms may be induced, such as local or generalized urticaria, or gastrointestinal and respiratory effects. In randomized studies that examined the effects of dietary exclusion in patients with AD, elimination of food allergens resulted

in improvement in AD in some patients.⁴² It should be noted that 5 foods—eggs, milk, soy, peanut, and wheat—are responsible for the highest percentage, 90%, of reactions in young children. If food allergy is suspected, then a limited trial of an exclusion diet can be considered once dietary assessment and advice by a pediatric dietitian has been given.⁴²

In a subset of patients, aeroallergens also trigger urticarial skin reactions. As had been demonstrated with food allergens, provocation with common aeroallergens, either by inhalation or direct contact, can cause immediate IgE-mediated reactions in the skin that might exacerbate AD.⁴³ Conversely, avoidance of aeroallergens that elicit positive patch test results or immediate hypersensitivity reactions might improve AD.^{20,44} Prevention of allergy through avoidance of aeroallergens also has been demonstrated. Halken et al⁴⁵ prospectively studied a series of infants at high risk for atopy from birth to 18 months of age. Recommendations were made to parents regarding infant diets and avoidance of common food allergens (either breastfeeding and/or hypoallergenic formula combined with avoidance of solid foods during the first 6 months of life), aeroallergens, and tobacco smoke. At 18 months of age, compared with a control group of high-risk infants, the prevention group had significantly lower cumulative prevalence of atopic symptoms. Therefore, in at least a subset of patients with AD, avoidance of food and inhalant allergens may improve clinical status. A prospective long-term study of a nonsedating antihistamine (cetirizine) showed a lower asthma prevalence in the subgroup of children with AD and IgE sensitization to pollens or house dust mites treated with cetirizine.⁴⁶

TREATMENT CONCEPTS IN AD

The most recent US guidelines for the management of AD were published by the American Academy of Dermatology in 1992.⁴⁷ Just as our knowledge of AD, asthma, and atopy has evolved, however, so,

too, have our treatment concepts. New information, new therapeutic options, and new models for treatment must be incorporated to enhance patient care and provide safe and effective treatment. The expert panel considered the following statements to be key concepts in the management of patients with AD.

Management of AD Should Recognize the Role of AD in the Atopic Diathesis

Because AD may be the entry point for the development of subsequent allergic disease, it is essential that clinicians across a spectrum of disciplines recognize that AD management must include comprehensive concerns about asthma, allergic rhinitis, and food allergy. Physician education and dissemination of the latest clinical findings are needed to raise awareness of the importance of AD management. The proper treatment of AD may prevent the progression of greater IgE production and the reaction in the skin, lungs, and nose.

Avoidance of Triggers Is an Important Goal in Patients With AD

Allergens may serve as triggers in a subset of patients with AD, and avoidance of allergens may improve or even prevent AD and other manifestations of allergic disease. Therefore, identification and reduction of triggers should be important goals of comprehensive management.

Therapeutic objectives for AD include

1. Induction of remission for acute skin inflammation
2. Inhibit or blunt flare development by early intervention with anti-inflammatory therapies to stabilize disease activity
3. Management: ongoing stability with safe dosing
4. Rescue: prompt therapy when breakthrough flares occur

In particular, the expert panel noted the importance of the concept of early intervention with anti-inflammatory agents to blunt inflammation at its earliest inception. It is expected that this concept of sustained early intervention in the inflammatory process will be a major advance in the standard management of AD. In asthma, this approach has been refined with guideline recommendations of daily maintenance inhaled corticosteroid therapy in mild, moderate, or severe persistent asthma.

Proper Skin Care in the Treatment of AD Is Essential

Regardless of the triggers of AD, errors in bathing and moisturizing are common causes of persistent AD. These errors contribute to inflammation by damaging the stratum corneum. This may increase transepidermal water loss, weakening skin barrier function. Appropriate education of patients and caregivers on skin care, including bathing and emollient use, is an important component of treatment.⁴⁸

New Therapies Give Us a Broader Spectrum of Opportunities

Current therapy for AD is aimed at hydration of the skin, reduction of skin inflammation, and the

relief of symptoms such as pruritus.^{37,48} A full range of available treatment options should be considered, with selection of treatments depending on the severity of AD. Treatments range from emollients to topical medications (corticosteroids, tacrolimus, pimecrolimus) to systemic agents (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), sedating antihistamines, and ultraviolet therapy.

Role of New Approaches and Emerging Treatments

The adverse effects of steroids (topical and systemic) in children have been a major concern for many physicians and parents and have stimulated a search for safer use regimens and for steroid-free treatments for AD. A recent study demonstrated that the use of intermittent steroids every other day is efficacious while further reducing the risk of side effects.⁴⁹ Promising emerging treatments are the macrolides tacrolimus and pimecrolimus, which are nonsteroidal immunomodulators. Their primary mechanism of action, which is distinct from topical corticosteroids, is to block the transcription of inflammatory cytokines in activated T cells through inhibition of the phosphatase calcineurin as shown in Fig 4.^{50,51} Although tacrolimus and pimecrolimus share the same primary mechanism of action, the small differences in molecular structure may influence characteristics of absorption and immunosuppression.

Topical tacrolimus, an ointment formulation of the oral systemic immunosuppressive agent used to prevent transplanted organ rejection, has demonstrated efficacy and safety in the treatment of AD. Tacrolimus acts locally via multiple cell types (eg, T cells, mast cells, dendritic cells). In animal models of allergic contact dermatitis, acute irritant dermatitis, and delayed-type hypersensitivity, tacrolimus reduced inflammatory skin reactions.

Tacrolimus influences the number of dendritic cells and the percentage of Langerhans cells in epidermal cell suspension from AD-affected skin, in addition to downregulating high-affinity IgE receptor expressions.^{50,52–57} In both short-term (12-week double-blind) and long-term (12-month open-label) clinical studies, topical tacrolimus has been shown to be an effective and safe for AD treatment in children and adults.^{50,56} Longer term safety data (2–3 years) for AD treatment in patients 2 to 15 years of age have been reported.⁵⁷ Longer duration of treatment did not increase the adverse event rate, and hazard rate analyses did not demonstrate local or systemic immunosuppressive effects.

Pimecrolimus, developed specifically as a cream for treatment of inflammatory skin diseases, has been shown to be effective and safe for AD in short-term (6-week double-blind) clinical studies in infants, children/adolescents, and adults.^{50,58,59} The long-term (12 months, pediatric patients; 6 months, adult patients) use of pimecrolimus was evaluated in 3 randomized, controlled, double-blind, multicenter trials in infants (3–23 months of age), children and adolescents (2–17 years of age), and adults (≥18 years of age) with mild to severe AD. In these long-term studies, a conventional therapy of emollients

Mode Of Action Of Macrolides: Inhibition Of Cytokine Transcription Mediated By NF-AT In Activated T-cells

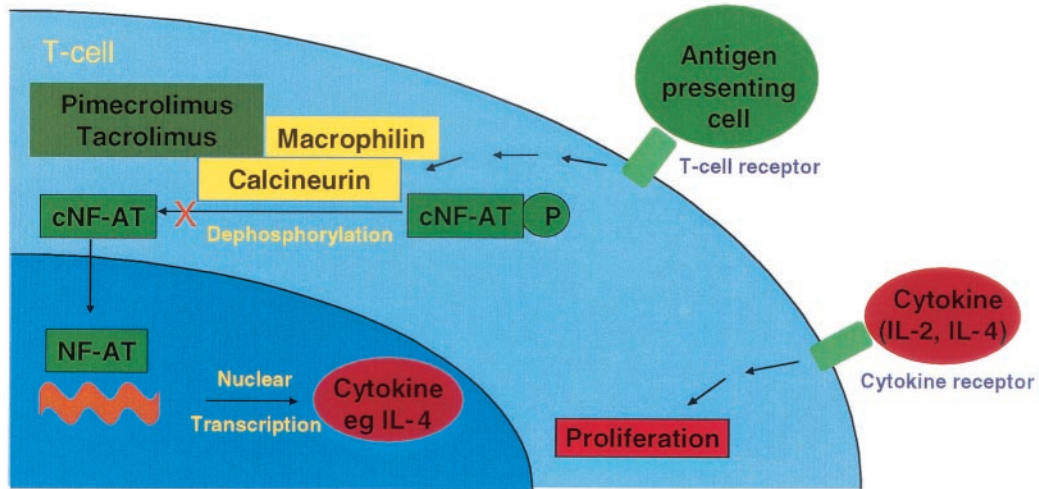


Fig 4. The mechanism of action of pimecrolimus and tacrolimus is to inhibit cytokine transcription mediated by the transcription factor NF-AT in immune and inflammatory cells.

for dry skin and a mid-potency topical corticosteroid used reactively to treat established flares was compared with pimecrolimus cream given twice daily from the earliest sign or symptom of AD, with mid-potency topical corticosteroid reserved for breakthrough flares.

During the first 6-month period, a greater percentage of those in the pimecrolimus group had no flares and required no topical steroids as compared with those in the control group in all age groups: infants (71% vs 39%; $P < .001$), children and adolescents (66% vs 38%; $P < .001$), and adults (45% vs 18%; $P < .001$). In each of the 3 studies, patients who were treated with pimecrolimus used significantly and substantially less corticosteroids than patients in the control group. In addition, those in the pimecrolimus group had significantly better disease control as indicated by sustained improvement from baseline Eczema Area and Severity Index score. The studies in infants and children/adolescents continued over 12 months, with data consistent with those obtained at 6 months.

The new steroid-free topical agents may offer an improved long-term management option to the topical steroid therapies alone that are currently offered to most patients with AD. However, the expert panel noted that there are still a series of unresolved questions that must be addressed to establish the role of these agents in AD therapy:

- Do these new agents have a different impact on long-term local cutaneous immunosuppression than topical corticosteroids?
- Can early, sustained treatment with these agents affect immune responses, particularly those involving primary cutaneous sensitization?

- Can these agents affect the development of skin cancer? (Recommendations for tacrolimus and pimecrolimus include sun avoidance and use of sunscreen/sun protection because of shorter time to squamous cell carcinoma development in a standard ultraviolet-irradiated mouse model.)
- What are selection criteria for use of these agents versus intermittent use of topical corticosteroids?

Regarding the use of combination steroid and/steroid-free agents:

- What is the optimal regimen for acute flares and long-term disease management?
- Is it appropriate for all patients?
- Is it more or less safe than either agent alone?
- Is it cost-effective versus current intermittent corticosteroid therapy?

Although, as with any new class of agents, a number of clinical questions remain, it is anticipated that these new steroid-free agents will play an important role in improving the short and long-term management of AD.

RATIONALE BEHIND THE RECOMMENDATION FOR AD TREATMENT GUIDELINES

The expert panel found a strong rationale for proceeding with the generation of treatment guidelines for AD. First, AD frequently is the first manifestation of an atopic diathesis that includes asthma and allergic rhinitis. Its position as the first disease in the atopic march requires enhanced awareness of AD with a new focus on the potential for progression to future IgE-mediated airway disease and food allergy. Second, good control of AD may theoretically

reduce the incidence and/or severity of asthma. It is theorized that successful disease modification is likely to require early treatment intervention in AD.

Although disease modification remains to be proved, in light of the medical and economic impact of the growing allergy epidemic, the potential for future disease prevention is extremely important. In addition, AD guidelines will do much to minimize inconsistencies in the treatment of patients across disciplines and will provide an important reference document for investigators of AD. Finally, AD guidelines will raise patient expectations and physician goals for treatment of this disease. The many parallels between AD and asthma provide reasons to examine the approaches outlined in the clinical practice guidelines for asthma, and to assess their relevance for the treatment of AD.

To assist health care professionals in bridging the gap between current knowledge and practice, the National Heart, Lung, and Blood Institute's (NHLBI's) National Asthma Education and Prevention Program convened 2 expert panels to prepare guidelines for the diagnosis and management of asthma. The initial panel, convened in 1989, was charged with the responsibility to develop a report that would provide a general approach to diagnosing and managing asthma based on current science. This report, *Guidelines for the Diagnosis and Management of Asthma*, was published in 1991. The recommendations for the treatment of asthma were organized around 4 components of effective asthma management:

1. Use of objective measures to assess disease severity and to monitor the course of therapy
2. Environmental control measures to avoid or eliminate factors that precipitate asthma symptoms or exacerbations
3. Comprehensive pharmacologic therapy for long-term management designed to reverse and prevent the airway inflammation characteristic of asthma as well as pharmacologic therapy to manage asthma exacerbations
4. Patient education that fosters a partnership among the patient and his or her family and clinicians

These guiding principles served as the starting point for 2 additional reports (NHLBI 1992 and NHLBI/World Health Organization 1995), both of which built on the original panel's recommendations.

The second expert panel, whose revised guidelines were published in 1997⁶⁰, expanded on the role of inflammation in asthma, as additional scientific evidence provided greater support of the concepts that asthma results from complex interactions among inflammatory cells, mediators, and cells and tissues resident in the airways. As in the case of the evolution of the asthma guidelines, this recent expert panel agrees that guidelines for AD will require the input of experts in dermatology, allergy, immunology, asthma, and pediatrics, as well as the leadership of national organizations whose missions include improvement of the care of patients with atopic disease.

CONCLUSION

The first expert panel report on the diagnosis and management of asthma had a tremendous positive impact for many aspects of asthma treatment. According to the second expert panel report, the original publication "redefined commonly held beliefs about asthma care, thus setting the stage for nationwide improvements in the clinical management of asthma and stimulating a variety of novel research."⁶⁰

The panel members who gathered to discuss the parallels between AD and asthma concluded that it is appropriate and timely to move forward with AD guideline development. It is hoped that the impact of such guidelines will be similar to those of the asthma guidelines and that they will form the basis for improvements in patient care and stimulate new research in AD therapy. Long-term tracking of outcomes related to therapeutic recommendations will be an important component to guideline modifications. It is essential that as our knowledge of atopic disease increases and our therapeutic options expand, our models for the treatment of AD will evolve accordingly.

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