

Dermatology Online Journal

Volume 9 Number 2

[DOJ](#)

[Contents](#)

Atopic Dermatitis

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Dermatology Online Journal 9(2): 1

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Abstract

Atopic dermatitis, the dermatologic manifestation of the atopic diathesis, has a variety of clinical presentations. This disease probably should be considered a syndrome—a group of signs and symptoms that frequently occur together in an identifiable pattern. The following update describes the spectrum of atopic dermatitis and summarizes current thinking about the etiology of the disease.

Introduction

Atopic dermatitis (AD), with its variable clinical presentations and course, constitutes a syndrome made up of an identifiable group of signs and symptoms that represents the dermatological manifestation of the atopic diathesis.

Despite some minor discrepancies and limitations in diagnosing AD, epidemiological studies continue to note AD as a fairly common problem, which in the past half century, has become more prevalent.[1,2] This increase in atopic diseases has been rationalized by a "hygiene hypothesis," which attributes the propensity toward the atopic-associated diseases to reduced microbial exposure in early life, especially in developed countries. [3] This increasing occurrence of AD, compounded by the managed-care mandate to deter specialists' consultations, subjects these patients to being managed by clinicians with less expertise. Despite the high incidence of AD, at a recent (January 2001) Consensus Conference on Pediatric Atopic Dermatitis, sponsored by the American Academy of Dermatology, 40 select physicians, including dermatologists and allergists (excluding pediatricians and other primary-care physicians), were only able to reach a weak consensus regarding the diagnosis, treatment, and required future research. Another, industry-sponsored (Novartis) conference, the International Consensus Conference on Atopic Dermatitis (ICCAD) held in New Orleans in February 2002, aspired to develop international guidelines, outlining current and forthcoming therapeutic options for the treatment of atopic eczema. They announced a consensus regarding the status of atopic eczema and overall treatment guidelines for atopic eczema. Even terminology has not become uniform. In Britain, AD is often referred to as atopic eczema (intrinsic and extrinsic types).[4,5,6] Ironically, there is some rationale to each of the proclaimed conclusions, and, because of the lack of a universal immunologic endorsement for all the differences, a general consensus will continue to evade us. The authors, a dermatologist-allergist (VSB) and an allergist (MB) intend to present objectively the current, significant available data regarding AD.

Epidemiology of atopic dermatitis

Epidemiology concerns the occurrence and the risk factors of a disease, and epidemiologic study can influence genetic counseling and research aims. Combining diverse expertise from the fields of epidemiology and human genetics provides unique opportunities to localize disease-susceptibility genes and examine molecular mechanisms of complex disease etiology.[7]

Until diagnostic criteria are standardized, validated, and applied universally, the true prevalence of AD will continue to be imprecise, thus varying between 10% and 30%. [1] Factors

contributing to the problem of determining prevalence are frequent remissions and unpredictable courses, especially in mild AD. Most of the population-based studies report that at least 80% of the AD populations have mild eczema.[8,9,10] Yet, recent studies using similar procedures and assessments demonstrate a definite trend toward the increase in AD cases in industrialized nations over the past few decades.[11,12] Newer treatment options have also changed the natural history of AD.[13]

Relatively few studies have focused on potential, initiating risk factors, but the strongest risk factor is a parental history of atopy or eczema. Maternal atopy is considered a greater risk for atopic disorders in offspring than paternal atopy.[14] AD and atopy in general seem to be diseases of the advantaged classes.[15] The prevalence of AD is inversely related to the number of siblings.[16] The larger the family size, the less the likelihood of having AD.

Etiology and pathogenesis

Diagnosis

Few clinicians have difficulty in identifying the patient with so-called typical AD. Recognizing AD in an infant with a very itchy, usually extensive, recurrent eczematous rash, whose family has had eczema, asthma or hay fever, is easy for most clinicians. However, the combinations and permutations generated by polygenic factors, modified by the varied individual phenotypic exposures endows each patient with an individual atopic fingerprint (profile) and results in a spectrum of clinical signs and symptoms.

Despite the ease physicians have in making the diagnosis of typical cases of AD, a consensus regarding specific diagnostic criteria still evades us, in part because of semantics and in part because of specialty-oriented bias. A clinically useful set of criteria for the diagnosis of AD includes the following: (1) atopy; (2) pruritus; (3) eczema; and (4) altered vascular reactivity. Any attempts to fine-tune these diagnostic features instigates intellectual dissension.

Each criterium is presented individually as part of the clinical manifestations of AD, below. Each feature's immunologic and physiologic implications is then discussed in order to better understand its occurrence and management.

Clinical manifestations

Atopy.— In 1923, Coca and Cooke coined the term "atopy" to describe the clinical presentations of type I hypersensitivity, which they noted in patients with asthma, hay fever, eczema, urticaria, and food allergies. Recent immunologic advances render that definition simplistic and imprecise.

Lack of an updated official definition for this term may be the major obstacle in reaching a consensus regarding the diagnosis of AD. Non-allergists recognize atopy in those patients with a family or personal history of asthma, hay fever, or eczema; allergists recognize atopy as an epiphenomena of immunologic aberrations, distinctive to a genetically predisposed population.

The authors propose an updated definition for atopy, as the expression of polygenic and phenotypic immunologic aberrations, with the potential for producing a spectrum of inflammatory reactions in various organ systems, initiated by the cytokinal profile of an induced transient effector Th1/Th2-cell reversal. These effector cells can be activated by immunologic and non-immunologic secretagogues. The atopic's propensity for a Th2 predominance produces IgE antibodies and attracts eosinophils with specific high-affinity IgE receptors. Hyper-releasable basophils and mast cells are also a typical feature. The combination of these features differentiates atopics with rhinitis, asthma, and eczema from non-atopics having some of the same symptoms.

Without the immunologic aberrations there is no atopy, and

assuming that one can have atopic dermatitis without atopy would be an oxymoron. It is the genetic predisposition of atopics to demonstrate a systemic expansion of Th2 cell activity, leading to releases of IL-5, IL-4, IL-13, and IL-3, which cause eosinophilia, increase IgE, and increase the growth and development of mast cells. Homing cutaneous lymphocyte antigen (CLA+) receptors on the surface of the Th2 cells induce the influx of inflammatory cells into the skin in patients with AD.[17] whereas the Th-cells of asthmatics cannot home to the skin because they are CLA-.[18]

Pruritus.— This most disturbing symptom must be considered both the quintessential feature and primary lesion of AD. The itch of AD is more than the result of an inherently lowered threshold; it is better considered as an innate perception of mild mechanical stimulation as itch and not as touch.[19] Once their pruritus begins, it increases the liability of the surrounding skin to react to light stimuli with itch--(em-dash)a phenomenon termed *allokinesis*, which is also noted in other pruritic dermatoses. As asthma is considered a twitchy lung syndrome, AD can be considered a twitchy skin syndrome. Whereas the ultrastructure of subepidermal and intraepidermal free nerve endings in patients with AD appear to be normal, Urashima et al. found the distribution density of the cutaneous nerve fibers to be much higher than in normal controls. [20] In addition, the diameter of the fibers were found to be much larger, owing to the increased number of axons in each nerve fiber. [20]

There is also increasing evidence that neuropeptides may be involved in the pathogenesis of AD. One of the first features of an exacerbation of AD is flushing of the affected skin and pruritus. Several neuropeptides have been identified as potent inducers of vasodilation and pruritus.[21] Scratching the skin releases Substance P from cutaneous proprioceptor nerves, which induces the release of histamine from mast cells in the scratched area. Elevated concentrations of histamine are found in the skin and plasma of patients with AD.

Several stimuli (secretagogues) are known to trigger the pruritus of AD. It has been demonstrated that all atopic patients have significantly greater irritant skin responses than nonatopic individuals.[22]

Some 63% of patients with AD rated their pruritus as very bothersome or extremely bothersome. Patients with moderately severe or severe AD considered pruritus as the symptom that most affected their health-related quality of life, and half these patients often or always experienced intolerable symptoms.[23] Eliminating or avoiding what provokes the pruritus should be the objective in the management of patients with AD.[24] The most commonly recognized triggers of itch in these patients have been reported to be the following: heat and perspiration (96%), wool (91%), emotional stress (81%), certain (usually vasodilatory) foods (49%), alcohol (44%), upper respiratory infections (36%), and house dust mites (>35%).[25,26] The recognized triggers of itch for AD are listed in Table 1.[27]

Table 1. Spectrum of "Triggers" of itch in AD

Not all patients with AD will be triggered by each stimulus. There are subsets of patients with AD who will experience exacerbations by some triggers and not by others.

<p>Xerosis</p> <p>Irritants</p> <ul style="list-style-type: none"> • Soaps, detergents • Disinfectants (e.g. chlorine) • Contact with <ul style="list-style-type: none"> ◦ Juices from fresh fruits, meats, vegetables, etc. ◦ Occupational chemicals, fumes, etc. <p>Contact-/Aero-allergens</p> <ul style="list-style-type: none"> • House dust mites (contact>aeroallergens)[28,29] • Pets (cats>dogs>birds)[30] • Pollens (seasonal) • Molds[31] • Human dander ("dandruff")[32]

Microbial agents [33]

- Staph. Aureus (as a pathogen or "superantigen")[34]
- Viral infections (esp. URI's)
- Mycologic
 - Pityrosporum[35]
 - Candida[36] (rarely)
 - Dermatophytes[37] (rarely)

Others

- Temperature/Climate[38]
- Foods[39] (as "contact" irritant>vasodilators>allergen)
- Psyche[40,41]
- Hormones[42]

The pathophysiology of the itch in AD is still not fully understood. Unlike urticaria, histamine is not believed to be the essential mediator of itch in AD.[43,44] Proteases, kinins, prostaglandins, neuropeptides, acetylcholine,[45] cytokines,[46] and opioids can cause itch or potentiate histamine release when injected into atopic skin.[47,48,49] Thus, the most effective and consistent antipruritics remain the systemic immunomodulators, glucocorticoids, cyclosporin A,[50] and calcineurin inhibitors,[51] as well as ultraviolet light therapy.[52] Although antileukotrienes, opioid antagonists, topical cromolyn, Chinese herbal therapy, and NSAIDs have all been reported to be helpful in some patients with AD, inconsistent results and faulty reporting deters physicians from prescribing them routinely. Antihistamines are used routinely even though conclusive, evidence-based evidence of efficacy is lacking.

Triggers of itch

Xerosis is considered to be the most common dermatosis of atopic individuals.[53] Xerosis can persist for life, independent of the activity of atopic symptoms, and seasonal variations are noted in 75% of patients.[20] The xerotic epidermis with its resulting barrier abnormality, provokes and sustains inflammation by activation of an epidermis-initiated cytokine cascade.[54,55] The impaired barrier function of atopic skin allows greater absorption of irritant agents and contact allergens. Further, easier access for bacteria, viruses, and dermatophytes has been demonstrated, and each of these can trigger the release of pruritogenic, pro-inflammatory mediators.

A marked decrease in the content of ceramide has been reported in the horny layer of the epidermis in AD.[56] Ceramide serves as the major water-holding molecule in the extracellular space of the horny layer, and this deficiency may be the primary cause of the characteristic dry and antigen-permeable skin of AD.[57] Preliminary results demonstrated a potential efficacy of a ceramide-dominant, barrier repair formulation in children with recalcitrant AD. The improvement was attributed to a normalization of barrier function, which in turn, dampened the cytokine cascade that sustains AD.[58]

Irritants readily have an excitatory effect on the impaired barrier layer of the atopic's skin. Daily washing with soap and water or noxious agents encountered at work and/or with hobbies can elicit an irritant contact reaction in atopic individuals.[59] Contact with wool is a common trigger of irritant contact dermatitis in AD. Woolen clothing, carpets, and blankets should be removed from each patient's environment. More than 80% of the skin-related cases of workers' compensation are noted in patients with a history of AD.[60]

Contact and aeroallergens.— Contact and aeroallergens are often suspected of being immunologic triggers of exacerbations, but, with the exception of animal dander and dust mites,[61,62] aeroallergens are rare causes of exacerbations of AD. Contact with dust mites is most often a cause in individuals whose eczema involves the face, head, neck, and hands (areas that come in direct contact with fomites).[63] In 1932, Rost was the first to report that patients with atopic eczema improved when they were placed in a dust-free environment,[64] a finding confirmed subsequently by

many investigators.[65,66, 67,68]

Infectious agents.— The altered skin barrier of atopic patients provides a portal of entry for various pathogens, which are weakly deterred by their aberrant immune systems.[69]

1. Bacteria. Increased staphylococcal skin colonization of affected and normal skin has been noted in patients with AD compared with controls.[70] *S. aureus* colonization can be demonstrated in over 90% of lesions with AD. The density of *S. aureus* on inflamed AD lesions without clinical superinfection can reach up to 10(7) colony-forming units per cm on lesional skin. Although the majority of patients with AD are colonized by *S. aureus*, its presence does not necessarily indicate that it acts as a pathogen; antibiotic treatment is indicated only when there is evidence of overt clinical infection or a superantigen effect is suspected.[71] Impetiginization is noted when there is a purulent oozing and crusting of the eczematous skin, and a superantigen reaction should be suspected when a generalized, serous-oozing, exquisitely pruritic, flare-up of the eczema is noted. Though not all studies agree, the importance of *S. aureus* is supported by the observation that these AD patients without obvious signs of a superinfection show a reduction in the severity of their skin disease when treated with a combination of antistaphylococcal antibiotics and topical corticosteroids.[72] Studies suggest that one strategy by which *S. aureus* exacerbates or maintains skin inflammation in AD is by secreting a group of toxins known to act as superantigens, which stimulate marked activation of T-cells and macrophages.[73]

2. Other bacteria, such as streptococcal species, may be important, but little clinical or investigative information exists to document their role.

3. Yeast. *Candida albicans* is the most common yeast, found in the mouth of 20%–25% of healthy adults, and regarded an opportunistic pathogen, or secondary invader of impaired skin, but there are no reports of increased or more severe *C. albicans* infections in patients with AD. However, positive skin prick tests with *C. albicans* occur more frequently in patients with AD than in normals. Yet it is unclear whether this response contributes to inflammation in AD.[74]

The lipophilic yeast, *Pityrosporon ovale* (*Pityrosporon orbicularis*) inhabits the seborrheic skin of most individuals, with a predilection for the neck, face, and upper trunk. Colonization is seen most commonly after puberty.[75] The presence of *P. ovale*-specific IgE antibodies have been found in 49% of patients with AD.[76] Patients with head, neck, and upper trunk distribution of AD lesions and evidence of specific antibodies to *P. ovale* have been reported to improve following antiyeast (ketoconazole) therapy. Postpubertal patients with refractory AD involving the head and neck warrant topical treatment with that agent. *Malassezia furfur*-specific IgE antibodies have been detected in the sera of some patients with AD.

4. Dermatophytes. Dermatophytes (e.g., *Trichophyton*) are suspected of occurring more frequently in atopic patients, a fact ascribed to their relative Th1 cell defect. However, there is only a single report suggesting that colonization can act as a trigger factor for AD.[77]

5. Viruses. Patients with AD do not have a major deficiency in defending against viruses. However, some viral skin infections can have a dramatic course. Kaposi's herpetiform and varicelliform eruptions, caused by spread of herpes and varicella viruses, are recognized as potentially dangerous complications of AD.[78] The effect of other viral infections on the course of AD is not uniform. Epstein-Barr virus, parainfluenza virus, respiratory syncytial virus, and cytomegalovirus infections have been reported to trigger exacerbation of AD.[79]

Foods.— Food allergy affects about 6%–8% of children younger than 4 years old and about 2% of the U.S. population beyond the first decade of life.[80] Food allergy remains the leading cause of anaphylaxis in the United States and many Westernized countries.[81] People who have these life-threatening

reactions usually have asthma and frequently have a history of AD and food allergy as young children.[82] For these reasons alone, the role of food as a trigger in all infants with moderately severe to severe AD should be considered.

Clinical studies addressing the role of food allergy in AD have shown that elimination of a relevant food allergen can lead to improvement in skin symptoms in a subset of patients with moderately severe to severe AD, and repeat challenge can lead to recrudescence of symptoms. In these individuals, disease can be at least partially prevented by prophylactically eliminating the more highly allergenic foods from the diets of infants and breastfeeding mothers.[83]

The prevalence of food allergy in patients with AD varies with the age of the patient and severity of AD.[84,85] The diagnosis of food allergy in AD is complicated by several factors: (1) the immediate response to ingestion of causal foods is down-regulated with repetitive ingestion, making obvious cause-and-effect relations by history difficult to establish; (2) various environmental factors (irritants, infection, other allergens) may play a role in the waxing and waning course of AD, obscuring the effect of dietary changes; (3) patients have a propensity to generate IgE to multiple allergens, many of which are biologically false positives, making a diagnosis based solely on laboratory testing unreliable. A general approach to the diagnosis of food allergy in patients with AD is presented in Table 2. However, not all food reactions in patients with AD are allergy based. Anything that increases blood flow through the skin (heat, febrile illness, normal hemodynamic diurnal variation) can generate itching in the atopic patient.[86] Vasodilatory agents that are ingested, such as alcohol,[87] spices, and hot drinks can cause itching, which leads to scratching and eczema, in patients with AD. Histamine-containing foods such as (aged) cheeses, very ripe vegetables (tomatoes, eggplant, spinach), and red wines (chianti, burgundy, and Concord grape) can all cause dry flushing leading to pruritus.[88]

Table II. General approach to evaluation of food allergy in AD

<p>Consider evaluation:</p> <ul style="list-style-type: none"> • Moderate to severe AD in infant/child • History of AD exacerbated by particular foods • Severe AD in in/adult <p>Initial screen</p> <ul style="list-style-type: none"> • History and physical examination • Skin/CAP-RAST to implicated foods (See Table III) • Common food allergens (milk, eggs, wheat, soy, peanut, tree nuts, fish, shellfish) Include history positive or suspected foods. Eliminate IgE+ foods from diet (and consider elimination of other highly suspected foods. <ul style="list-style-type: none"> ○ No resolution: Food allergy not a cause ○ Resolution: Food allergy potential cause. <p>Physician-supervised oral food challenges for suspected foods (unless previous severe reaction)</p> <ul style="list-style-type: none"> • Open, single-blind or double-blind, placebo-controlled challenges • Add back foods as indicated from challenge results • Periodic repeat challenge to monitor resolution of allergy.

Psyche.— AD can have a profound effect on an individual's social interactions, psychologic adjustments, work success, sexual relationships, and quality of life. Although the burden of chronic illness is easy to identify and its consequences are apparent, the relationship between AD and psychologic symptoms is neither simple nor one-sided.[89]

Stress increasingly has been recognized as an important factor in the pathogenesis of AD, but responses to stress are variable and dependent on the existing psychologic foundation of the patient and family. Stressful events often have been observed to occur

before an AD exacerbation.[90,91] Children with AD have been shown to be more susceptible to stress-induced skin eruptions because of a hyporesponsive hypothalamus-pituitary-adrenal axis, which blunts the body's natural ability to produce cortisol and suppress inflammation in response to stress.[92]

The presence of AD causes anxiety and depression. Evidence that mood disturbances increase and decrease as a result of fluctuation of disease severity can be found in studies demonstrating that mood symptoms correlate with AD symptoms and decrease following successful AD treatment.[93,94]

In the immune system, neuropeptides are involved in the integration of intrainmune regulation and in the bidirectional communication between the immune and the neuroendocrine systems. Neuropeptides are ubiquitous throughout the body. When the higher cortical centers are activated by stress, there is an increased secretion of Substance P from the adrenal glands.[95] Centrally, they serve as brain peptides that are easily released by psychosocial stress, triggering or exacerbating itching, especially in patients with AD.[96]

Climate.— Atopic patients have an abnormal pattern of thermoregulation, which is believed to reflect an intrinsic disturbance of the parasympathetic system, which can influence the activity of AD.[97] Most patients are aware of seasonal variations in their AD; most improve in summer and worsen in winter.[98] However, heat- and exercise-induced sweating can trigger an exacerbation at anytime of the year.[99]

Vocks et al. found that itch intensity in patients with atopic dermatitis was correlated with certain meteorological variables. A clear-cut inverse correlation was noted with air temperature, but the effects of humidity, air pressure, and hours of sunshine were less pronounced.[100] They concluded that a certain range of thermohygric atmospheric conditions with a particular balance of heat and water loss on the skin surface is essential for the skin of atopics to feel comfortable.

Hormones.— One third of young female patients reported premenstrual flare-ups of their AD in a questionnaire study.[101] Pregnancy also was noted to have an adverse effect on 52% of pregnant patients with AD, during the first and second trimester, but improvement was noted in the third trimester.

Vaughn-Jones et al. in a prospective study of 200 pregnant women found a surprisingly high prevalence of eczema. Hormonal analysis showed a significant reduction in serum cortisol levels compared with nonpregnant controls.[102]

Eczema is a clinical symptom and not a specific diagnosis. All eczemas are histologically spongiotic, but not all spongiotic dermatoses are clinically eczematous! The term *eczema* is derived from the Greek meaning "boiling over", which is identified macroscopically by the presence of vesicles (bubbles), and histologically as intercellular edema (spongiosis). Thus the histology of any eczema is nonspecific, and the differential diagnosis of the clinical symptom must be deliberated. The clinical differential diagnosis of the eczemas can be separated into pediatric and adult diseases. (Table 3)

Table III. Clinical Differential Diagnosis of Eczema

Pediatric	Adult
<ul style="list-style-type: none"> • Wiskott-Aldrich Syndrome • Hyper-IgE Syndrome • Ataxia-telengectasia • Agammaglobulinemia • Hartnup's Syndrome • Acrodermatosis enteropathica • Scabies • Seborrheic Dermatitis • Phenylketonurea 	<ul style="list-style-type: none"> • Allergic Contact Dermatitis • Irritant Contact Dermatitis • Seborrheic Dermatitis • Cutaneous T-Cell Lymphoma • Psoriasiform eruptions • Pityriasis rubra pilaris • Scabies • Glucogonoma Syndrome

- Pellagra

The clinical and histological similarities between the various eczematous disorders strongly suggest a common effluent pathway. T-cells seem to be the principal effector cells of eczematous conditions, yet significantly different infiltration patterns of T-cell subsets are noted in each dermatosis. Human T-cell subsets can be classified by their reaction to clusters of monoclonal antibodies on their surface:

Table IV: Cluster Designation

Cell Surface	T- Cell Subset/Function
CD1	Cortical thymocytes
CD2	Pan-T-cell (E-rosette receptor)
CD3	Mature T-cells
CD4	Helper T-cells, inducer (most common DTH subset)
CD8	T cytotoxic, suppressive subset, (also DTH subset) (DTH delayed-type hypersensitivity)

The mean T-helper(CD4+) cells/mean T-suppressor(CD8+) cell ratio of the papillary dermal infiltrate is highest in AD; whereas the epidermal infiltration of T-cells is lowest in AD.[103]

CD4+ T-cells are further divided into Th1 cells (which produce IL-2, IFN- γ , TNF- β , and Th2 cells (which produce IL-4, IL-5, IL-10, IL-13).[104] The specific pro-inflammatory mediators released from each subset, result in the spectrum of clinical presentations. Bullous and vesiculobullous lesions, which are pathognomonic for Th1-driven allergic contact dermatitis, are never seen in Th2-driven acute lesions of AD.

The Characteristic clinical features of the eczema of AD

1. Age of onset. Some 60% of patients develop AD within the first year of life, 85% by age 5.[105] Early onset often indicates a more severe course.

AD affects infants, children, and young adults predominantly.

2. Distribution. AD has been called the itch that erupts, rather than the rash that itches. This statement is not quite true. In reality AD is the itch that, when scratched, erupts. Patients with AD whose extremity is placed in a cast for weeks do not develop eczema under the cast.[106] Thus, scratching or rubbing itchy, atopic skin characterizes this eczema as being isomorphic. Its distribution is variable and age-related, with a distribution that corresponds to areas of the body that are accessible to scratching and rubbing.[107] Yet, the nose is almost always spared and is referred to as the head-light sign. The diaper area is usually spared.

The distribution of AD is almost exclusively isomorphic.

3. Clinical appearance. The eczema is polymorphic, with acute (oozing, or crusted, eroded microvesicles on papular, erythematous plaques), subacute (thicker, paler, somewhat scaly, erythematous, excoriated plaques), and chronic (lichenified, more scaly, hyperpigmented, excoriated, papular plaques) forms. It is not unusual for each stage of evolution to be present at the same time in an individual patient with AD. The dermatitis is more likely to be generalized during infancy and childhood, and more apt to be localized in older individuals. Localized AD has been erroneously labeled as dermatitis confined to specific areas, such as eyelid dermatitis, nipple dermatitis, palmar-plantar dermatitis, cheilitis, and pityriasis alba.[108]

4. Course. AD is a chronic dermatosis, characterized by exacerbations and remissions. Most exacerbations can be attributed to one of the triggers of itch. Many cases resolve by age 2, and improvement by puberty (with or without any treatment) is

common. It is rare to see AD after age 50.

AD is persistent, but relapsing, characterized by exacerbations and remissions.

Localized variants of AD.— Separating localized variants of eczema of AD seems unwarranted, because any eczema that itches in an atopic individual should be considered part of the spectrum of AD. Localization merely exemplifies the isomorphic response.

Eyelid dermatitis.— The prevalence of atopy as the cause of eyelid dermatitis remains conjectural because of the individual bias of each reporting investigator.[109] Svensson's review of the literature reported an incidence of 8%–23% of atopic patients with predominantly eyelid involvement.[110] The vulnerability of the thin eyelid skin, which is constantly exposed to irritants (i.e. tobacco smoke) and allergens, combined with its accessibility to rubbing perpetuates its chronicity.

Typically, atopic eyelid dermatitis presents as symmetrical, pruritic, scaly erythematous or hyperpigmented, lichenified, papulovesicular plaques that are usually first noted at the upper-medial aspect of the eyelids. With continued scratching, the entire orbital skin becomes involved. Scratching and rubbing often results in loss of eyelashes or eyebrows, a finding that, when associated with xerosis, causes health-care workers to evaluate for hypothyroidism. In patients with persistently acute eczema, a possible allergic or irritant contact dermatitis must be considered. Important allergens include topical corticosteroids, other topical medications, or house dust mites.[25] Secondary impetiginization is a rare occurrence.

Palmar and plantar dermatitis.— When 2452 newly hired hospital workers were studied, the incidence of the development of hand eczema was three times higher in those who were atopic.[111] In addition, hand eczema has been noted to occur in 70% of children with AD.[112] Atopy has been reported to occur in up to 57% of patients with juvenile palmar-plantar dermatosis.[113]

Eczema on the palms and soles presents as a glistening erythema with varying degrees of scaling and fissuring. Lichenification results from the constant rubbing of the xerotic palmar and plantar skin. The dorsum of the hands may or may not be similarly involved. The non-weight-bearing areas of the soles and interdigital spaces are spared. Sparing of the interdigital spaces should defer consideration of a possible dermatophytic infection. The condition runs a chronically relapsing course with worsening in winter, but persistent lesions are noted in approximately 40% of patients.[114]

Pityriasis alba.— presents as finely scaling, hypopigmented, poorly demarcated, macular plaques. Initially the patches may be mildly inflamed; histologically, spongiosis is noted.[115] Sites of predilection include the face, neck, and upper trunk. It has been reported to occur in 20%–44% of atopic children, with or without other evidence of AD.[116] These hypopigmented lesions become more apparent after UV exposure. Mycologic evaluation is occasionally warranted to rule out tinea versicolor or a dermatophytosis.

Cheilitis.— Cheilitis is noted as a persistent scaliness, usually restricted to the vermilion, but often extending onto the perioral skin. It often starts in the winter during childhood and appears as dry scaly lips and often attributed to frequent licking to hydrate the dryness. Rarely is eczema noted, yet the lips may appear edematous and the vermilion is covered with visible ichthyotic scales. Contact with various foodstuffs perpetuates the dermatitis. Secondary candidal infection is rare, and angular cheilitis is more often associated with facial AD, especially in patients that hypersalivate.

Nipple dermatitis.— Nipple dermatitis is noted in 12%–23% of patients with AD.[117] It is most common in postpubertal girls. The very sensitive areolar skin koebnerizes with the slightest rubbing or friction of clothing. It is frequently symmetrical, scaly, oozing, and papulovesicular, and it may extend onto the adjacent

breast skin.

Infra-auricular, retro-auricular, and infranasal fissuring.—

In these areas AD presents as an asymmetrical plaque of fine, scaly, excoriated, macular and papular erythema with fissuring in the folds. The inflammatory component is usually the result of secondary bacterial infection. The infra-auricular fissuring has been deemed pathognomonic for AD (Hertoghe's sign).[118]

Vulvar dermatitis.— Vulvar dermatitis presents as a circumscribed, scaly, erythematous lichenification of the labia and pubic triangle. It is triggered by the severe pruritus of the very sensitive skin. In females it is at times the only manifestation of AD. Because of self-medication, allergic or irritant contact dermatitis must always be considered, especially in poorly responsive, therapeutically persistent cases.

Altered vascular reactivity.— Although altered vascular reactivity is a very characteristic feature of atopic individuals, it is almost always ignored. This paradoxical vascular reactivity is common. Of AD patients, 50%–60% have facial pallor,[119] and up to 60% demonstrate white dermatographism,[120] a paradoxical vasoconstriction elicited by lightly stroking the skin (there is no wheal formation). This same reaction can be elicited in atopic individuals when acetylcholine or methacholine is injected intradermally, or nicotinic acid is applied topically.[121] Redness is seen in nonatopic individuals. Thermal sweating abnormalities are exemplified by the fact that heat-stroke- and exercise-induced cholinergic urticaria is seen almost exclusively in atopic individuals.[122] Sulzberger noted a vicious cycle of sweat retention and dermatitis in patients with AD.[123] Sweating has been reported to be a trigger of itch in 96% of patients with AD.[124] Pronounced vasoconstriction on exposure to cold, and low finger temperatures have also been noted in atopic patients.

Nonessential features of atopic dermatitis

Were eczema the only skin finding of AD, the label atopic eczema would deserve merit; however, eczema is but one of many specific skin findings noted in atopic patients, with and without AD. Thus the term dermatitis is more appropriate to encompass the entire spectrum of cutaneous changes. The noneczematous skin findings, which include xerosis, keratosis pilaris, so-called allergic shiners, Dennie-Morgan lines; palmar and plantar hyperlinearity, periorbital milia, anterior neck folds, and several eye findings, are considered nonessential for the diagnosis of AD, because they can be seen in nonatopic patients.

Xerosis.— Xerosis is recognized as finely scaling, clinically noninflamed skin, which is usually generalized. Often recognized at birth, xerosis persists throughout the patient's life, independent of the activity of other atopic symptoms. Some 75% of afflicted patients note a seasonal variation, tending to improve during the more humid, warmer weather and worsening during the dry, winter weather.[125]

Atopic skin not only appears but also feels dry and is the result of a genetic decreased ability for the atopic keratinocytes to bind water. A markedly increased transepidermal water loss has been demonstrated.[126,127] Because this xerosis is not the result of abnormal keratinization, it is not ichthyotic and does not show large fish-scale plaques. In fact, atopic facial skin usually appears fine and smooth. These findings, combined with a decreased sebum production,[128] often result in a milder, teen-age acne.[129] Yet, elimination of the lipophilic organism *Pityrosporon* has resulted in the improvement of facial eczema in some adolescents.[130]

Aggressive lubrication of atopic skin not only decreases the trigger for itch but also improves the barrier layer against irritant and contact allergens.

Keratosis pilaris.— Keratosis pilaris is regarded as a defect of keratinization at the xerotic hair follicles, in which the follicular openings are filled with horny plugs making the skin feel like sand paper or chicken skin. It occurs in 55% of atopic patients with or

without AD (and in 15% of nonatopic patients). It is frequently noted during childhood, peaks during adolescence, and becomes less apparent during adulthood.[131] It is most often noted on the extensor aspects of the upper arms, thighs, buttocks, and face. Keratosis pilaris is essentially asymptomatic but cosmetically disturbing to teenagers. Perifollicular accentuation is more noticeable in pigmented individuals.

Allergic shiners.— The term refers to periorbital darkening. Allergic shiners are asymptomatic, symmetrical, blue-grey discolorations of the periorbital skin and (check #) are most apparent below the orbit. It has been reported to occur in up to 60% of atopic patients and in 38% of non-atopic individuals. There is a tendency for the orbital darkening to fade with age, and it is often seen in other atopic family members. It seems to be associated with chronic nasal congestion in both atopic and nonatopic patients. [120]

Dennie-Morgan lines.—Dennie-Morgan lines are symmetrical, prominent folds, extending from the medial aspect of the lower lid. It is seen most often in patients with Down's syndrome, and in 60%–80% of atopic individuals. These folds are usually present at birth, or appear shortly thereafter, and persist for life.[132]

The incidence of ocular involvement in AD, reported in the ophthalmologic literature is between 25% and 42%[133].

Vernal conjunctivitis.— Vernal conjunctivitis is a severe bilateral, recurrent, chronic inflammatory process of the upper eyelid conjunctiva.[134] It is most frequently noted before age 10. Its classical symptoms include intense pruritus, exacerbated by all the usual triggers of AD-related itch.

Atopic keratoconjunctivitis.— Atopic keratoconjunctivitis is almost always associated with AD. Its always bilateral, and the sometimes disabling symptoms include itching, burning, tearing, and heavy, mucoid discharge. It is frequently associated with eyelid dermatitis and chronic blepharitis.[134]

Anterior capsular cataracts.— Anterior capsular cataracts tend to develop during adolescence or early adult life. The anteriorly located and shield-shaped cataracts are pathognomonic for AD. They are nearly always bilateral. The incidence of these cataracts has been reported to be from 3% to 10% and has been associated with keratoconus in some cases.[135]

Keratoconus.— Keratoconus is a conical deformity of the cornea. It is believed to occur 10 times more often in patients with AD than in controls and is believed to result from the increased rubbing of the eyes in patients with eczema and allergic rhinitis.

Palmar and plantar hyperlinearity.— Palmar and plantar hyperlinearity is recognized as exaggerated dermatoglyphics of the palms and soles. Although these markings become more visible when the skin is dry, it is not believed to be a result solely of xerosis. It is seen more often in atopics than nonatopics.

Periorbital milia.— Periorbital milia are intraepidermal inclusion cysts resulting from the plugging of facial sebaceous ducts. They appear as asymptomatic, 1-2 mm, dome-shaped, white or yellowish papulonodules, occurring individually or in clusters periorbitally. The white milium body is composed of lamellated keratin. It is also seen as a result of continuous topical corticosteroid therapy.

Anterior neck folds.— Anterior neck folds are noted as prominent, horizontal folds running across the middle of the anterior neck of some atopic patients. Like the Dennie-Morgan lines, they are asymptomatic and have no clinical significance.

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