Current Views of Atopic Dermatitis

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Atopic Dermatitis (AD) is one of the most intensively researched allergic disease in recent years. The readily available tissues led us understand the cell trafficking, allergen presenting to our immune system, T helper cell polarization, and allergic inflammation. The similar pathophysiologic mechanisms may apply to other allergic disease like asthma and allergic rhinosinusitis.

Atopic dermatitis is a chronic inflammatory skin disease that is considered familial with allergic features. It often occurs in patients with other atopic disorders such as asthma and allergic Rhinitis. The terms "dermatitis" and "eczema" are frequently used interchangeably. When the term "eczema" is used alone, it usually refers to AD (atopic eczema). "Eczematous" also connotes some scaling, crusting, or serous oozing as opposed to mere erythema.

EPIDEMIOLOGY — The atopic disorders affect 8 to 25 percent of populations worldwide and the incidence of allergic diseases and AD appear to be increasing. They may occur in any race or geographic location, although there appears to be a higher incidence in urban areas and developed countries, especially western societies. The vast majority of AD has an onset before age five years, and prevalence data in children show a slight female to male preponderance (1.3 to 1).

PATHOGENESIS — The precise immunologic mechanisms involved in the pathogenesis of AD are not completely understood, and there is no marker for the disease. The importance of allergic triggers is suggested by the observation that approximately 85 percent of patients have elevated serum IgE concentrations and positive immediate skin test results to a variety of food and inhalant antigens. Food allergies are rare in adults, but avoidance of aeroallergens, particularly dust mites and animal danders, has resulted in clinical improvement in some patients with AD.

1. Genetic Factors: A genetic basis for AD is suggested by the following:

- Almost 50 percent of patients with AD report a family history of respiratory atopy.

- Scandinavian studies have found that a monozygotic twin of an affected twin partner has a higher risk of the disease than a dizygotic twin partner; the risk in the latter is similar to that of ordinary siblings.
- Chromosome studies have suggested that the trait for atopy may be inherited via a maternal gene located on chromosome 11; clinical studies demonstrate a higher risk for atopy if a child's mother rather than father has atopy. Linkage on chromosome 3q21, 1q21, 17q25, and 20p also have been reported; all of these loci correspond closely with known psoriasis loci.

2. Skin barrier dysfunction

AD is characterized by dry skin, even involving nonlesional skin and increased transepidermal water loss. In particular, ceramides serve as the major water-retaining molecules in the extracellular space of the cornified envelope, and the barrier function of these complex structures is provided by a matrix of structural proteins, which are bound to ceramides. A reduced content of ceramides has been reported in the cornified envelope of both lesional and nonlesional skin in patients with AD. Changes in stratum corneum pH levels have been found in patients with AD and might impair lipid metabolism in the skin. Overexpression of stratum corneum chymotryptic enzyme is also likely to contribute to the breakdown of the AD epidermal barrier. This would allow penetration of irritants and allergens, which trigger an inflammatory response, thus contributing to the cutaneous hyperreactivity characteristic of AD. The increased susceptibility to irritants in patients with AD might therefore represent a primary defect of epidermal differentiation compounded by the presence of inflammation-induced skin damage.

The Itch-Scratch Cycle: Scratching or rubbing the skin can make the itch and rash of AD worse. Scratching causes further irritation, injures the skin, and increases itchiness. This is called the itch-scratch cycle.

3. Allergens

- **Food.** Placebo-controlled food challenge studies have demonstrated that food allergens can induce eczematoid skin rashes in a subset of infants and children with AD. In some patients urticarial reactions can trigger the itch-scratch cycle that flares this skin condition. Children with food allergy have positive immediate skin test responses or serum IgE directed to various foods, particularly egg, milk, wheat, soy, and peanut. Food allergen–specific T cells have been cloned from the skin lesions of patients with AD, providing direct evidence that foods can contribute to skin immune responses. In addition, it is well established that food can exacerbate AD both through allergic and nonallergic hypersensitivity reactions. Furthermore, direct contact with the skin (eg, in the preparation of meals or when feeding infants) might be an important factor for the aggravation of eczema.

- **Dust Mites & Aeroallergens.** Beyond the age of 3 years, food allergy is frequently outgrown, but sensitization to inhalant allergens is common. Pruritus and skin lesions can develop after intranasal or bronchial inhalation challenge with aeroallergens in patients with AD. Epicutaneous application of aeroallergens (eg, house dust mites, weeds, animal danders, and molds) by means of the APT on uninvolved skin of patients with AD elicits eczematoid reactions in a subset of patients with AD. A combination of effective house dust mite reduction measures has been reported to improve AD. The isolation from AD skin lesions and allergen patch test sites of T cells that selectively respond to Dermatophagoides pteronyssinus (Der p 1) and other aeroallergens supports the concept that immune responses in AD skin can be elicited by inhalant allergens.

4. Microorganisms

Superantigens: Most patients with AD are colonized with S aureus and experience exacerbation of their skin disease after infection with this organism. In patients with AD with bacterial infection, treatment with antistaphylococcal antibiotics can result in reduction of skin disease. An important strategy by which S aureus exacerbates AD is by secreting toxins called **superantigens**, which stimulate activation of T cells and macrophages. Most patients with AD make specific IgE antibodies directed against staphylococcal superantigens, which correlate with skin disease severity. Superantigens also induce corticosteroid resistance, thereby complicating their response to therapy.

Antimicrobial peptides deficiency (e.g. defensins): AD skin has also been found to be deficient in antimicrobial peptides needed for host defense against bacteria, fungi, and viruses. This constellation of genes is underexpressed because of the significant upregulation of TH2 cytokines in AD (e.g. IL-4). Along with lower levels of proinflammatory cytokines, such as TNF-α and IFN-γ, the decrease in antimicrobial defenses within patients with AD might explain their increased susceptibility to skin infections compared with that seen in patients with psoriasis.

Patients with AD have an increased propensity toward disseminated infections with herpes simplex or vaccinia virus. Susceptibility to severe viral infections, such as eczema herpeticum or eczema vaccinatum, might be linked to the severity of atopy. As such, smallpox vaccination is contraindicated in patients with AD unless there is imminent danger of exposure to smallpox.

There is increasing evidence that the opportunistic yeast Malassezia species represents a contributing factor in AD. Several studies have demonstrated the presence of specific serum IgE, a positive skin prick test (SPT) response, and a positive APT response against Malassezia species in adults with AD. IgE sensitization to Malassezia species is specific for patients with AD but is not seen in patients with asthma or allergic rhinitis.

On the other hand, the gut microflora may be a natural source of immune modulation that prevents atopic disease. In one study, administration of a probiotic containing a Lactobacillus strain prenatally to pregnant women who had at least one first-degree relative (or partner) with atopic eczema, and postnatally for six months

to their infants, resulted in a significant reduction in the frequency of atopic disease in the children compared with administration of placebo (23 versus 46 percent). Exclusive breast feeding during the first three months of life also has been associated with a lower incidence of AD during childhood in children with a family history of atopy.

5. Irritating Factors:

- **Irritants:** An irritant is something that causes burning, itching or redness. Almost anything can be irritating to the skin when the rash of AD is severe. Chemicals, solvents, soaps, detergents, fragrances, some ingredients in skin care products, some fabrics, and smoke are irritants the patients may need to avoid.
- **Temperature and Humidity:** Cold weather, heat and sweating may make AD worse. Extremes of temperature and humidity can be a problem for people with AD. Sweating caused by overheating and high humidity can irritate the skin. Low humidity causes water to be lost from the skin. This can lead to dryness and skin irritation.
- **Emotions and Stress:** Emotions and stress do not cause AD, but they may bring on itching and scratching. Anger, frustration and embarrassment can cause flushing and itching. Day to day stresses as well as major stressful events can lead to or worsen the itch-scratch-itch.

CLINICAL MANIFESTATIONS AND DIAGNOSIS — Most patients have manifestations of AD by age five to seven years. In children, acute skin lesions that appear as intensely pruritic erythematous patches with papules and some scaling can be seen on the face, scalp, extremities, or trunk; diaper areas are usually spared.

Acute lesions can include vesicles and there can be serous exudate in severe cases. The skin lesions in older individuals with more chronic disease are characterized by thickened skin, increased skin markings (lichenification), and excoriated and fibrotic papules. In adults, the flexural areas (neck, antecubital fossae, and popliteal fossae) are most commonly involved; other common sites include the face, wrists, and forearms. In severe cases, any area of the body can be involved, although it is uncommon to see lesions in the axillary, gluteal, or groin area; lesions in these locations should prompt consideration of other diagnoses such as psoriasis. The presence of pustules within areas of dermatitis suggests secondary infection with Staphylococcus aureus.

The diagnosis of AD is predominantly clinical; there are no objective diagnostic tests. Pruritus, a chronic recurring course of dermatitis, a positive family history of atopy, and the early age of onset are the most important features that suggest the diagnosis. The distribution and collection of skin findings is more important than the appearance of individual lesions. Other physical findings that support the diagnosis of AD include xerosis (dry skin), infraorbital skin folds (Dennie Morgan lines), periorbital darkening, hyperlinear palms (accentuation of fine palmar skin lines), and keratosis pilaris (follicular accentuation that is usually present on the extensor surfaces of the upper arms).

Differential diagnosis — The differential diagnosis of AD includes other eczematous disorders such as contact dermatitis, seborrheic dermatitis, and drug reactions. In infants, considerations include psoriasis, scabies, Wiskott-Aldrich syndrome, and hyperimmunoglobulin E syndrome.

TREATMENT

1. Skin Care: Maintaining skin hydration is the most critical therapeutic goal of the management of AD.

"Soak And Seal": Maintaining skin hydration — Evaporation of water on the skin leads to xerosis in patients with AD; skin hydration is a key component of their overall management.

- Take at least one bath or shower per day. Use warm, not hot, water for at least 15-20 minutes. Avoid scrubbing your skin with a washcloth.
- Use a gentle cleansing bar or wash such as Dove®, Oil of Olay®, Eucerin®, Basis®, Cetaphil®, Aveeno® or Oilatum®.
- Gently pat away excess water (within 3 minutes of a bath or shower). Apply the moisturizer or the special skin medications onto the damp skin. This will seal in the water and make the skin less dry and itchy.
- Apply special skin medications to the areas affected with rash that is red and/or scaly. The most common skin medications used to treat the skin inflammation are topical steroids or topical immunomodulators (TIMS). Used correctly, these medications are safe and effective.
- Apply moisturizer everywhere on the skin which has not received medication. Moisturizers are available in many forms. Creams and ointments are more beneficial than lotions. Vaseline® is a good occlusive preparation to seal in the water; however, it contains no water so it only works effectively after a soaking bath.

2. Enviromental Control:

A. Reduce skin irritation

- Avoid scratching or rubbing the skin. This can make the itch worse. Apply moisturizer whenever the skin feels dry or itchy.
- Wash all new clothes before wearing them. This removes formaldehyde and other potentially irritating chemicals which are used during production and packing.
- Add a second rinse cycle to ensure removal of soap, if you are concerned. Residual laundry detergent, particularly the perfume or dye, may be irritating when it remains in the clothing. Changing to a liquid or milder detergent may also be helpful.
- Wear garments that allow air to pass freely to your skin. Open weave, loose-fitting, cotton-blend clothing may be most comfortable. Avoid wearing wool.
- Work and sleep in comfortable surroundings with a fairly constant temperature and humidity level.
- Keep fingernails very short and smooth to help prevent damage due to scratching.

- Appropriate use of sedating antihistamines may reduce itching to some degree through their tranquilizing and sedative effects.
- Use sunscreen on a regular basis and always avoid getting sunburned. Use a sunscreen with an SPF of 15 or higher. Sunscreens made for the face are often less irritating than regular sunscreens.
- Residual chlorine or bromine on the skin after swimming in a pool or hot tub may be irritating. Take a quick shower or bath immediately after swimming, washing with a mild cleanser from head to toe, and then apply an appropriate moisturizer.

B. Dust Mites & Aeroallergens Avoidance:

- Wash all blankets, sheets, pillowcases, and mattress pads, if used, in hot water (130º) every two weeks.
- Encase mattress and box spring in zippered allergen-impermeable covers.
- Encase comforters and pillows in zippered allergen-impermeable covers or wash every two weeks in hot waters (130°).
- Use wipeable furniture (wood, plastic, vinyl or leather) in place of upholstered furniture.
- Remove carpeting if at all possible.
- Take steps to reduce carpet allergen levels:
- Vacuum weekly using a mask.
- Use vacuum cleaner with HEPA filter.
- Mites grow best at 75-80% relative humidity but cannot live at less than 50% humidity. Take steps to reduce humidity:
- Use air conditioning.
- Use dehumidification units.

3. Diet Elimination: In pediatric population, avoidance of certain foods can be helpful. Common food triggers include eggs, nuts, peanut butter, chocolate, milk, seafoods, and soya.

4. Medication

- **Corticosteroids** — A low potency corticosteroid cream or ointment (eg, 1 or 2.5 percent hydrocortisone) is effective for patients with mild AD. A medium potency corticosteroid ointment (eg, triamcinolone 0.1 percent) may be needed for those with more severe disease. Higher potency topical corticosteroids can be used for up to 10 days in some patients with acute flares, and then replaced with lower potency preparations until the lesions resolve. Potent steroids (class I-IV) are generally avoided in skin folds and on the face; however, limited brief use of potent steroids may produce a rapid response after which patients can be switched to lower potency preparations. An acute exacerbation of chronic AD can sometimes be aborted by a short course of systemic corticosteroids (eg, prednisone 40 to 60 mg/day for three to four days, then 20 to 30 mg/day for three to four days).
- **Controlling pruritus** — Antihistamines are widely used as a therapeutic adjunct in patients with AD to treat both pruritus and eye irritation. The

sedating antihistamines appear to be most effective (eg, diphenhydramine, hydroxyzine, and cyproheptadine), although nonsedating preparations such as fexofenadine or loratadine may also be useful. Higher than normal doses may be necessary. Doxepin, a tricyclic antidepressant with potent H1 blocking properties, is valuable as a second-line antihistamine if others fail. Tepid baths to hydrate and cool the skin can also temporarily relieve itching.

- **Topical calcineurin inhibitors** — The topical calcineurin inhibitors appear to be effective for the treatment of AD, and, unlike topical corticosteroids, do not cause skin atrophy. For this reason they may be particularly useful on the face, neck, and in skin folds. Tacrolimus and pimecrolimus are applied twice a day.

    i. **Topical tacrolimus** is an effective alternative to topical corticosteroids. In addition to its inhibitory effect on cytokine production, topical tacrolimus causes alterations in epidermal antigen-presenting dendritic cells that may result in decreased immunologic response to antigens. The efficacy of tacrolimus has been demonstrated in several randomized, controlled trials. Unlike topical corticosteroids, tacrolimus ointment does not cause skin atrophy, which may provide an advantage for patients with facial disease. Tacrolimus has been used successfully in patients with refractory eyelid disease. Transient burning, erythema, and pruritus are the most common adverse effects.

    ii. **Pimecrolimus cream**, 1 percent, is a calcineurin inhibitor like tacrolimus that was developed specifically to treat inflammatory skin conditions. Its mechanism of action is similar to topical tacrolimus, and it does not appear to have systemic immune effects.

    iii. Several clinical studies suggest that tacrolimus ointment, particularly the 0.1 percent preparation, may be somewhat more effective than pimecrolimus cream, though it may also cause somewhat greater local irritation.

    iv. Safety — Although in controlled trials the topical calcineurin inhibitors have appeared to be safe in adults and children. In 2005, based upon case reports, animal studies, and the known risks with systemic calcineurin inhibitors, the FDA issued warnings about a possible link between the topical calcineurin inhibitors and cancer, and in 2006 placed a "black box" warning on the prescribing information for these medications.

5. Other therapies — The management of severe AD that is resistant to conventional therapy is a challenge and frequently requires the help of a dermatologist. A number of alternatives are available:

- Ultraviolet light therapy (phototherapy) with PUVA (psoralens plus ultraviolet A radiation), UVA, UVB, or narrow-band UVB are successful in controlling AD. However, these therapies are expensive ($25 to $100 per

treatment), and may lead to an increased risk of melanoma and nonmelanoma skin cancer. Thus, treatment with this modality is limited to severe cases.

- Occasionally immunosuppressants such as methotrexate, azathioprine, or mycophenolate mofetil may be used. These therapies should be prescribed by a dermatologist and are generally avoided in children.
- Patients with pustules should be evaluated with bacterial cultures and treated with appropriate oral antibiotics.
- Topical preparations containing cromolyn sodium may provide some benefit.
- Probiotic therapy with Lactobacillus and other organisms has been studied for the treatment of AD in infants,but is probably not of significant benefit. Oral essential fatty acid supplementation also does not appear to be beneficial.
- There have been case reports of improvement in refractory cases with the anti-IgE monoclonal antibody omalizumab.

SUMMARY AND RECOMMENDATIONS — Atopic dermatitis is a chronic inflammatory skin disease that is considered familial with allergic features. In children, acute skin lesions that appear as intensely pruritic erythematous patches with papules and some scaling can be seen on the face, scalp, extremities, or trunk; diaper areas are usually spared. The skin lesions in older individuals with more chronic disease are characterized by thickened skin, increased skin markings (lichenification), and excoriated and fibrotic papules. In adults, the flexural areas (neck, antecubital fossae, and popliteal fossae) are most commonly involved.

A key feature of AD is severe dryness of the skin caused by a dysfunction of the skin barrier with increased transepidermal water loss. This is typically accompanied by intense pruritus and inflammation. The regular use of emollients is important for addressing this problem, and together with skin hydration, it represents the mainstay of the general management of AD. Emollients should be applied continuously, even if no actual inflammatory skin lesions are obvious.

Education to enhance disease knowledge, psychologic improvement in disease perception, and scratch control behavior modification, together with regular daily treatment, will lead to better skin care. This improvement in disease control will restore family dynamics, and the patient and family will cope better and have an overall improvement in quality of life. Additionally, education should be aimed at reducing doctor shopping, facilitating a better partnership between the doctor and the patient-parent, and decreasing the long-term costs of chronic disease treatment.