Atopic dermatitis: addressing allergy, infection, itch and complementary therapies

Jusleen Ahluwalia, MD;1,2 Dawn Marie Davis, MD;3 Sharon Jacob, MD;4 Andrea Waldman, MD;1,2 Peter Y Ong, MD;5 Stuart Cohen, MD;6 Adam Friedman, MD;7 Peter Lio, MD;8 Nathan Jetter, BS;9 Jeffrey Bienstock, MD;10 Jennifer LeBovidge, PhD;11 Jonathan Spergel, MD, PhD;12 and Luz Fonacier, MD13

Abstract
Atopic dermatitis (AD) is a complex condition that results from the dynamic interplay between genetic predisposition, skin barrier defects, environmental factors, and a dysfunctional immune system. As a result, AD can be complicated by irritant and allergic contact dermatitis and imbalances in the skin microbiome, which can subsequently exacerbate the severity and complicate the course of preexisting atopic disease. Itch is an important symptom of AD, as it plays a large role in the quality of life of patients and their families. Since AD is a chronic, inflammatory disease that recrudesces throughout life, many have utilized alternative and/or complementary therapies, as monotherapy or in conjunction with conventional therapies, as a form of management.

Semin Cutan Med Surg 36:112-117 © 2017 Frontline Medical Communications

Topic dermatitis (AD) is a chronic or relapsing, inflammatory condition characterized by pruritic, eczematous plaques, usually with a specific morphology and/or distribution. Although primarily considered a pediatric disease, AD affects a significant number of adults as well, either as persistent disease from childhood or as adult-onset or recurrence of AD. It has the potential to cause significant distress for both patients and their families. Because the pathogenesis of the disease is multifactorial and largely dependent on the interplay between environmental triggers, immunologic factors, and skin barrier dysfunction, patients with AD are susceptible to insults from multiple factors such as irritants, allergens and imbalances in microbiome diversity. This review summarizes allergy, infections, itch in AD and discusses various alternative and complementary therapies.

Food allergies and atopic comorbidities
Food allergies are considered a common trigger for atopic dermatitis. But, in fact, they are a very rare trigger in adults and an uncommon trigger in pediatrics. The percentage of individuals with food-induced atopic dermatitis varies with the severity of AD in pediatrics. Approximately 5% of the pediatric patients with mild AD have a food allergy trigger, and this number increases to 20% in moderate to severe AD.1 Patients with AD can have elevated IgE, leading to false-positive results and unnecessary food avoidance if screening is done for general patients with AD. Therefore, the NIAID guidelines recommend testing for food allergies in only individuals that cannot be controlled with standard medical therapies.2 However, AD is a risk factor for food allergy and often precedes food allergy. Similarly, the more severe AD patients have more food allergy (25%) compared to mild AD (8%).3 The risk factor for AD is based on human and animal models show that sensitization through eczematous skin leads to food allergies. This was proven in a pivotal trial led by Lack that showed early peanut introduction in children with atopic dermatitis led to a decrease in the prevalence of peanut allergy4 and subsequent revised NIH guidelines recommending introduction of peanut in the first year of life.5

AD is also considered the start of the atopic march, with the development of asthma and allergic rhinitis commonly occurring after AD. It is well established that the severity of AD increases the likelihood of these other diseases.1 Seasonal allergies or allergic rhinitis is seen in about 50% of adults with atopic dermatitis and asthma is seen in 40% of patients with moderate atopic
dermatitis. Similar rates have been observed in pediatric studies, with 33% having allergic rhinitis and 38% having asthma and allergic rhinitis in an observational study of 2270 children with AD. In theory, the control of atopic dermatitis may prevent the development of asthma and allergic rhinitis, indicating the importance of treatment of AD (refer to discussion in Davis et al, Diagnosis, Comorbidity, and Psychosocial Impact of Atopic Dermatitis in this issue).

Allergic dermatitis

Historical perception premised that patients with AD had decreased susceptibility to developing allergic contact dermatitis (ACD) due to the predominant Th2-helper 2 response, rather than Th-helper 1 delayed mediation response. Current evidence suggests an underestimated impact of contact sensitization on AD and reveals fundamental elements that increase susceptibility in AD. One critical factor is the impaired skin barrier function confounded by the repeated application of topical therapeutics to restore the barrier, which can notably contain potential allergens. Potential allergens include emulsifiers, preservatives, solvents and other additives (eg, fragrances). Occlusion in a moist environment, as indicated in patients with AD, prolongs contact between skin and allergic material (dyes, finishes, surfactants, etc). This is especially relevant because certain haptenes (small molecular weight chemicals) readily penetrate barrier-compromised skin.

Data have indicated that AD patients are as likely as the general population to develop ACD, with metals, fragrances, topical antibiotics/antiseptics (eg, neomycin, bacitracin, and cleaners). MI is often used in combination with MCI (methylisothiazolinone [MI]), emulsifiers (propylene glycol, sorbitans, lanolin) and fragrance-based chemicals such as Compositue (chamomile). Topical antibiotics/antiseptics (eg, neomycin, bacitracin, benzalkonium chloride) are also frequently implicated as sensitizers. Nickel is the most common sensitizer in asymptomatic children. In a study, 12.9% of children (aged 6-67.5 months) were positive patch test to nickel. Several risk factors for development of nickel allergy include body piercings (sustained contact with releasable nickel in the setting of a wounded barrier) and bacterial colonization, which upregulates inflammatory mediators that play a role in the development of contact sensitization.

Emollients are frequent sensitizers, which commonly include preservatives (formaldehyde-releasing preservative [FRPs], benzoxates, methylisothiazolinone [MI]), emulsifiers (propylene glycol, sorbitans, lanolin) and fragrance-based chemicals such as Compositue (chamomile). Topical antibiotics/antiseptics (eg, neomycin, bacitracin, benzalkonium chloride) are also frequently implicated as sensitizers in patients with AD. Prevalent surfactant allergens include cocamidopropyl betaine, amidoamine, and dimethylpropylamidoamine. Disperse dye allergy has also been reported from textiles (uniforms).

Isothiazolinone contact allergies are frequent across all populations. These preservatives are commonly used in cosmetics and toiletries and in household products such as shampoos, detergents, and cleaners. MI is often used in combination with MCI (methylchboroisothiazolinone), and is commonly referred to as Kathon CG. The neck and flexural areas of limbs were frequently involved in those with positive patch test reactions to nickel and Kathon CG. Methylisothiazolinone has been reported to cause systematized reactions in AD patients.

Patch testing is an indispensable element of eczema diagnosis to identify region sensitizers in both ACD and AD, as not all flexural dermatitis is AD. Clinical relevance of positive patch test reactions is critical. Allergen avoidance is the definitive method to assess relevance and is the mainstay of treatment.

Infection

It is well known that patients with AD have a high frequency of bacterial, viral, and fungal infectious complications, largely due to skin barrier dysfunction and immune dysregulation. Keratinocytes do not only serve as a physical barrier, but also play a role in generating immune responses as a first-line defense. Keratinocytes upregulate antimicrobial peptides (AMPs), which are essential in directly suppressing microbial pathogens in addition to signaling the immune system through the production of cytokines and chemokines. In AD, barrier defects allow the penetration of allergens and infectious agents, which are then presented by dendritic cells to upregulate the Th2 pathway and thus the inflammatory cascade. Moreover, increased pH promotes reproduction and adhesion of pathogenic microbes.

Adaptive immunity has also been implicated in activating the inflammatory response in infected AD patients. In affected areas, plasmacytoid dendritic cells (DCs), which are vital in combating viral infections, are lacking. Conversely, Langerhans cells (LC) are increased, which, when activated, aids in Th2 polarization. Th2 response yields an upregulation in IL-4, IL-5, IL-10, and IL-13. The latter phase of inflammation is characterized by IFN-y, IL-12, and GM-CSF, which characterize the Th1 response. These cytokines and subsequent responses are important in the pathogenesis of AD and culminate in immune dysfunction.

The skin microbiome is dependent on skin pH and functionality of keratinocytes. Commensal bacteria, such as S. epidermidis and S. hominis, in particular, play a role in immunomodulation. By secreting inhibitory proteins that suppress the growth of pathogenic bacteria, the normal microbial composition can prevent colonization and infection. Thus, compromise of the skin barrier, changes in pH, and immune dysfunction set the stage for infection in AD patients.

S. aureus is a saprophytic bacteria detected in 5%-30% of normal skin. The carriage rate of S. aureus is 76% of nonlesional skin, and 93% of lesional skin of AD patients. S. aureus is the most common skin infection in AD, which can potentially lead to severe and invasive bacterial infection, such as sepsis, endocarditis, and septic arthritis. Its enterotoxins A-E, also known as superantigens, contribute to the pathogenicity of S. aureus as they act as allergens. These superantigens bind as intact proteins to T-cell receptors and MHC class II molecules to activate T cells to produce inflammation at both the local and systemic level. S. aureus is also known to produce high levels of serine proteases, which are known to degrade the skin barrier.

Patients with AD are susceptible to MRSA, with prevalence of MRSA colonization ranging from 11% to 34%. It has been hypothesized that AD patients colonized with MRSA tend to be corticosteroid resistant because Staph superantigens compete with the beta isofrom of the glucocorticoid receptor. If the infection is limited to localized areas, topical antibiotics, such as mupirocin, may be indicated. However, if the lesions are widespread, oral antibiotics are warranted. Intravenous antibiotics are required for invasive infections. If there is a history of MRSA colonization or a family history of MRSA infection, evaluation and decolonization for MRSA must be considered.

Eczema herpeticum (EH) affects approximately 3% of AD patients and is caused by herpes simplex virus (HSV). EH is characterized by clusters of multiple, uniform, 2-3 mm crusted papules,
and vesicles may develop in untreated or poorly controlled AD. The initial infection may be accompanied by fever, malaise, and lymphadenopathy. Because staphylococcal alpha toxin promotes viral replication in keratinocytes, *S. aureus* infections may be associated with AD patients who have been infected with EH. Those who develop EH tend to have a greater Th2 response when compared to AD patients who do not develop EH. It has been noted that cytokines that are invoked by the Th2 response are thought to inhibit antiviral defense mechanisms.

Genetics may also render an AD patient vulnerable to EH. For example, mutations in TSLP and signal transducer and activator of transcription 6 (STAT6) are associated with EH in patients with AD. Moreover, genetic differences in specific interferons and their receptors are associated with an increased risk of developing EH. Filaggrin mutations have a stronger association in AD patients who develop EH when compared with those who do not develop EH.

Viral culture swab or PCR methods can be used to diagnose HSV. Depending on the extent of involvement and virulence of the infection, therapy can range from oral to intravenous acyclovir. Ophthalmology consultation for eye involvement may be indicated. Because most EH patients may have secondary bacterial infections, coverage with antibiotics should be considered.

Patients with underlying AD can present with vesicles and erosions within lesional areas and can also have coxsackie virus infection that has been termed eczema coxsackium (EC). The demographics reveal a predilection for preschool-age children, with infections primarily occurring from late spring to early summer. EC is associated with the relatively common hand, foot, and mouth disease (HFMD), which has been linked with CVA16 infection. However, whereas oral erosions and gray-white vesicles predominate within an acral distribution in HFMD, EC is superimposed on AD lesions and on the buttocks. Many also have associated fever and constitutional symptoms. A positive lesional PCR for enterovirus confirms the diagnosis of EC. Viral culture for CVA6 is not recommended as the virus does not grow well in culture. Treatment is supportive with an appropriate skin care regimen.

Eczema vaccinatum (EV) is a complication of smallpox vaccination that is caused by live vaccinia virus in smallpox vaccine administered to AD patients. This infection manifests as a rapidly developing, generalized vesiculopustular rash with systemic illness. EV can have a significant mortality rate ranging from 5% to 40%. The intrinsic qualities of the poxvirus combined with the immune dysfunction of AD can render a patient more prone to EV. The virus replicates in skin with preexisting inflammation, as hyperplastic keratinocytes promote viral replication. Moreover, the virus can stimulate production of epithelial growth factor and thus cause keratinocytes to enter mitosis phase, further promoting viral infection. Because the use of smallpox vaccine has not been frequent for several decades, cases of EV have not been frequently encountered. However, because of the concern that smallpox (variola) virus may be used as a biological weapon, military smallpox vaccination has resumed since 2002. As a result of careful screening to exclude AD patients, only rare cases of EV have been reported in the recent years. EV patients are reported to CDC for treatments with vaccinia immunoglobulin and antiviral drugs.

Molluscum contagiosum virus (MCV) favors infection in the skin of AD patients, and has been referred to as eczema molluscatum (EM). Clinically, up to hundreds of umbilicated flesh-colored papules affect both lesional and nonlesional skin of AD (likely through autoinoculation). MCV inhibits the immune response and down-regulates natural killer cell and T-cell activation through release of inhibitor proteins against chemokines. Since most lesions are self-limited, EM may be managed with observation alone. However, cases with severe pruritus may warrant treatment with cantharadin, cryotherapy, curettage, or topical agents.

Recent studies have revealed that the fungi compose 1% to 22% of the normal skin microbiome, the most common species being *Malassezia*. *Malassezia* spp rely on exogenous lipids for their metabolic requirement. *Malassezia* spp, as part of the normal skin microbiome, interact with cutaneous dendritic cells or lymphocytes. However, the mechanism of interaction between *Malassezia* spp and host cells remains unclear.

Many AD patients are sensitized to *Malassezia* spp, which may correlate with the severity of disease. Several trials have investigated the role of topical or systemic antifungals in AD patients, although, with equivocal results. Several trials investigating the efficacy of ketoconazole topically applied to head and neck AD showed a decrease in *Malassezia* colonization, but no improvement in clinical severity.

Other data revealed that oral itraconazole treatment in AD patients improved head and neck AD lesions and reduced the need for topical corticosteroids. Candida yeasts are also part of the normal flora of mucosal surfaces. More than 50 different candida species have been identified. *Candida* spp have been cultured more often from normal-looking and lesional skin in AD patients when compared with healthy individuals. However, the impact of *Candida* spp on clinical severity is unclear. Chronic dermatophyte infections are also common in patients with AD, and likely play a role as allergens. Similar to that of *Candida* spp, the data regarding the association of AD with chronic dermatophyte infections remains ambiguous.

**Pruritus**

Pruritus (itch) in AD is usually severe and has a huge impact on the patient’s quality of life. Pruritus is an unpleasant sensation that elicits the urge to scratch. Sensation of pruritus can be triggered by endogenous and exogenous stimuli that activate specific peripheral un-myelinated C-fiber nerve endings in the dermis and epidermis. The pruritogenic stimulus is then signaled along the dorsal root ganglion via the spinal cord before crossing to the contralateral spinothalamic tract reaching different areas of the cortex. The scratching reflex is initialized in the motor cortex. The central nervous system modulates the perception of “itch” and triggers the desire to scratch. In lamina 1 of the dorsal horn, the gastrin-releasing peptide receptor plays a role in mediating itch sensation in the spinal cord. Cutaneous pruritogens include histamine, proteases, neuropeptides, acetylcholine, neurotrophin-4, cytokines, platelet activating factor, endothelin, and certain leukotrienes and cytokines.

Patients and families report the itch-scratch cycle to be the most significant aspect of coping with eczema, with the impact on quality of life comparable to that of chronic pain. Children display increased irritability and fussiness when itchy, and greater itch intensity has been associated with depressed mood in teens and adults. Patients and families experience helplessness and frus-
tation around controlling the itch, and parent-child conflict over scratching is common. Because psychological stress is a known trigger of itch and skin flares, the emotional stress of having eczema can exacerbate the condition, creating a vicious cycle. Sleep disturbance is reported in over 60% of children and adults with eczema, including difficulty falling asleep, nighttime awakenings, reduced sleep efficiency, and daytime tiredness. Sleep disturbance in turn can negatively affect daytime functioning, including mood, behavior, concentration, and cognitive functioning. Parental sleep is also disturbed, with 50% of parents co-sleeping with children to reduce nighttime scratching.

Primary therapy to treat AD-associated itch includes identification and elimination of trigger factors, maintaining the skin barrier through emollients, and addressing psychological and behavioral components. Elimination of trigger factors includes avoiding activities that lead to pronounced sweating and avoiding exogenous factors such as contact with wool and exposure to aerallergens (including dust mites, pollen, and animal dander) and foods that have been identified as triggers. Symptomatic management of itch may entail treatment with topical emollients, corticosteroids, calcineurin inhibitors, and crisaborole. Other antipruritic topicals include menthol, capsaicin, topical antihistamines, topical naltrexone, and N-palmitoylethanolamine.

Oral medications to reduce itch include systemic anti-inflammatory agents and antipruritic agents. Treatments targeting the anti-IL-31 receptor A or anti-IL-4 receptor alpha have been promising in research settings. Conventional therapies for atopic dermatitis are available to reduce atopic itch; however, the results have been equivocal. Patients may benefit from a multidisciplinary approach to itch management, including psychological and behavioral interventions such as relaxation training, stress management, trigger identification, and habit reversal (substitution of competing responses when the urge to scratch arises).

**Alternative and complementary therapies**

It is thought that more than half of patients with AD have tried an alternative type of therapy. Alternative medicine encompasses treatments that have not amassed sufficient evidence, or have evidence to suggest that they are ineffective, and thus remain outside the cannon of conventional therapy. Challenges arise when some treatments may not be safe or regulated to ensure safety, and when some treatments are difficult to test in controlled settings. Yet, there are a few treatments that have at least some evidence of safety and efficacy. Conventional health care practitioners are reluctant to recommend many of these treatments, as the paucity of scientific studies supporting them often means a lack of clinical consensus on their optimal use. Nevertheless, it is worthwhile to consider some of these as adjuncts to traditional medical therapy, as eczema can be a chronic and debilitating condition for many, and simple awareness to some of the commonly discussed therapies can help address patient concerns.

Vitamins and probiotics are often recommended during patient encounters with alternative practitioners. Such vitamins include topical B12, oral vitamin D, pyridoxine, zinc phosphate, selenium, sea buckthorn seed, and hempseed oil. There are many disparate studies, and often contradictory findings. For example, a study by Camargo et al showed that vitamin D supplementation improved winter-related AD among Mongolian children, a population likely to have vitamin D deficiency in winter. Another study by Hata et al, a multi-center, placebo-controlled, double-blind study in 30 pts with AD and 30 non-atopics randomized to 4,000 IU of D3 or placebo, found no significant change in eczema severity scores. These 2 examples demonstrate some of the confusion in this area, and nicely illustrate the difficulties in the entire category of alternative and complementary treatments.

Preliminary data investigating the clinical utility in ingesting probiotics in AD patients have been supportive; however, additional data is needed to support its efficacy, as well as to determine ideal strain(s), dosage, and frequency of administration.

Food exposure has been implicated as a trigger for an AD flare. Oftentimes dairy, gluten, sugar, and/or dye-free diets are recommended to AD patients. There may be certain foods that significantly contribute to atopic flares and have been proven by a double-blind, placebo-controlled challenge to exacerbate a patient’s AD. However, these are usually limited to a few identified foods, and current evidence is scarce concerning the efficacy of any particular diet in controlling eczema symptoms, except for avoiding foods one is truly allergic or sensitive to. Current guidelines discourage the avoidance of particular foods unless they are verified allergens that exacerbate AD.

Herbal therapy has a long history, particularly in Asian countries. Certain plant extracts, in the form of tea or tinctures, or creams and lotions, can be used to reduce inflammation associated with AD. In 2004, a Cochrane review discussed collective evidence for herbal medicine in AD. Although a trend toward positive benefit was observed, recommendations regarding the use of herbal medicine in AD could not be made, as most studies were small. For example, a small randomized control trial showed significant efficacy in more than half the children who used Chinese herbal treatments for AD when compared with the placebo group.

Acupuncture and acupressure have been modestly successful in reducing pruritus in patients with AD. These methods are based on the belief that ill health is the result of poor flow of “qi” (energy) along meridians (energy channels). Stimulating certain points along these meridians can result in improvement of symptoms and better health. Fine needles, often not much thicker than a hair, are inserted into prescribed points and, if performed correctly, is a painless and relaxing process.

Massage therapy is a gentle technique that has been shown to reduce stress and anxiety around AD and may also help with the skin itself. Benefits of massage therapy include improved circulation, stimulation of the parasympathetic nervous system to evoke a relaxation response, and elevated mood through endorphin release. Massage using a carrier oil specifically chosen for eczema-prone skin may also have the effect of improving the condition of the skin. Two small studies demonstrated improvement in AD severity in pediatric patients with or without oils applied to skin with massage techniques.

Hypnotherapy may influence the subconscious to aid healing and reduce the inflammation of eczema. A small RCT demonstrated a significant decrease in body surface area involved in pediatric patients with AD who were treated with hypnotherapy, when compared with a control group; however, results were similar to those receiving biofeedback. Another small study showed that adults with AD resistant to conventional treatments demonstrated significant improvement in symptoms while on hypnotherapy.
Aromatherapy is defined as the use of oils to produce a physiological and/or psychological effect through olfaction. Treatment is often combined with massage techniques. Certain essential oils have properties that may help heal skin damaged by eczema. For example, German chamomile and yarrow reduce inflammation, while lavender and helichrysum may promote new cell growth. Tea tree and manuka honey may play a role in the prevention of infection. Oils such as calendula, coconut, and borage are rich in fatty acids that may help rebuild a weakened skin barrier system. One study showed a significant improvement in the massage therapy group (with or without aromatherapy) but there was no significant difference between the aromatherapy and massage-only groups.

Several complementary approaches in the management of AD have been described, mostly as adjuvant modalities in conjunction with topical conventional agents. Stress may be a key factor in promoting immune dysfunction. Thus, relaxation may have a positive effect on patients’ quality of life by means of reducing stress, yet there is little evidence to support its impact on the clinical severity of AD.

There are many possible alternative therapies, and many questions remain. Pending further investigation, it is best to seek a knowledgeable guide for recommendations regarding these treatments.

References
13. Hegewald J, Uter W, Pfahlberg A, Geier J, Schnuch A; IVDK. ...