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SAIGE I: *Staphylococcus aureus*, Immunological, Genetic, and Environmental (SAIGE) Factors Contributing to Atopic Dermatitis and the Use of Ceramide-Containing Skincare

Lawrence A. Schachner MD FAAD FAAP,[a] Anneke Andriessen PhD,[b] Latanya Benjamin, MD FAAD FAAP,[c] Mercedes E. Gonzalez MD FAAD,[d] Pearl Kwong MD FAAD FAAP,[e] Peter Lio MD FAAD,[f] Robert Sidbury MD MPH,[g] Nanette B. Silverberg MD FAAD[h]

[a]Dermatology and Pediatrics, Pediatric Dermatology, University of Miami School of Medicine, Miami, FL
[b]Radboud Academy; Radboud UMC, Nijmegen and Andriessen Consultants Malden, The Netherlands
[c]Young Skin MD, Florida Atlantic University, Parkland, FL
[d]Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine Miami, FL
[e]Apex Clinical Trials/Suncoast Skin Solutions, Jacksonville, FL
[f]Northwestern University Feinberg School of Medicine, Chicago, IL
[g]Seattle Children's Hospital; University of Washington School of Medicine Seattle, WA
[h]Mount Sinai West and Mount Sinai Beth Israel, New York, NY

ABSTRACT

Background: Atopic dermatitis (AD) is a common heterogeneous disorder that typically starts in infancy and early childhood, is associated with the development of comorbidities, and may persist into adulthood. Skin barrier dysfunction is a pivotal contributor to AD and is impacted by *S. aureus* colonization and immunological, genetic, and environmental (SAIGE) factors. Managing AD in clinical practice remains challenging due to multiple contributing SAIGE factors.

Methods: A global expert panel of 7 pediatric dermatologists and dermatologists used a modified Delphi process comprising face-to-face discussions and an online follow-up to define five consensus statements providing recommendations based on the literature, clinical experience, and the panel's opinion for healthcare providers treating pediatric patients with AD.

Results: The panel defined SAIGE factors that compromise skin barrier function and contribute to AD development. The recommendations focus on the impact of SAIGE factors in pediatric AD development, reducing exposure to modifiable risk factors to mitigate skin barrier dysfunction. Continuous skincare that is initiated from birth may delay and mitigate AD, specifically in high-risk populations.

Conclusions: According to panel consensus, recognizing and mitigating SAIGE factors and initiating ceramide-containing skincare from birth are important. The panel recommendations underscore the need for clinician education to improve knowledge of the impact of SAIGE factors and therapeutic mitigation strategies to delay flare development and reduce AD severity.

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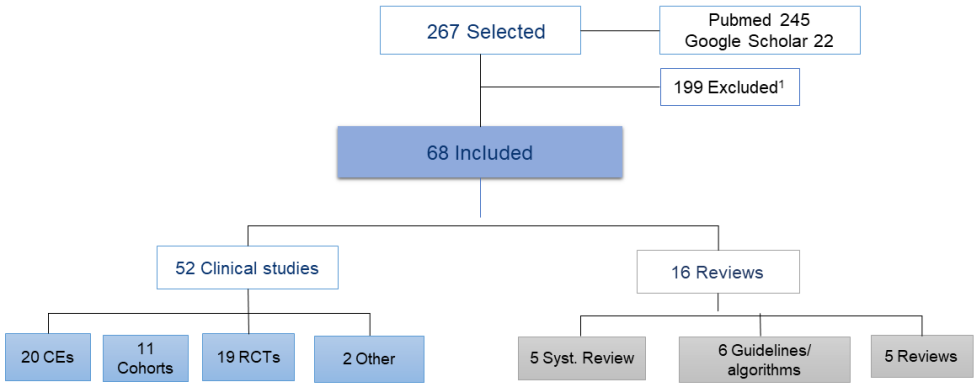
INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease typically with onset in infancy or early childhood and may persist into adulthood, with a prevalence of up to 20% in the pediatric population.[1,2] It remains unclear if AD is a single disease or a spectrum of diseases with a shared phenotype.[3] Certain clinical features are highly characteristic of AD, including eczematous lesions, xerosis, pruritus, relapsing course, and inherited atopy.[1,3,4] AD is associated with pruritus, sleep disturbance, and reduced quality of life (QoL).[1,2,4] AD has the highest disease burden among skin disorders globally and is associated with an 8.3-year reduction in lifespan and $250 million in healthcare costs in the United States.[5,6]

Despite advances in topical and systemic AD treatment options, challenges persist in AD management, leading to substantial disease impact on patients and caregivers.[7] Approximately 2 million outpatient visits annually are due to AD, where dermatologist visits are more frequent for chronic AD, and primary care physician (PCP) visits are more frequent for acute AD, particularly in pediatric patients less than four years old.[7,8] AD has a profound impact on pediatric patients as well as secondary effects on caregivers, highlighting the need for improved AD management and disease control, especially in pediatric patients.[9]

FIGURE 1. Systematic literature search results.



Grading of clinical studies on skincare:
A = Randomized, double-blind clinical trial of high quality
B = Randomized clinical trial of lesser quality
C = Comparative trial with severe methodologic limitations
1 = Further research is unlikely to change confidence in the effect
2 = Further research is likely to change confidence in the effect
3 = Further research is very likely to change the effect
4 = Any estimate of effect is very uncertain.

Duplicates, not including SAIGE factors or skincare, poor quality. *S. aureus*, Immunological, Genetic, Environmental (SAIGE), Clinical Evaluation (CE), Randomized controlled trial (RCT)

AD poses a significant unmet medical need for a single therapy effective against all AD severities and symptoms and approved in all patients, including pediatric patients.8-9 Effective AD management should control inflammation and flares, minimize pruritus and xerosis, reduce secondary infection, and include skin barrier restoration and protection.[2]

This manuscript identifies 4 clusters of SAIGE (*Staphylococcus aureus*, immunological, genetic, and environmental) factors impacting skin barrier function and AD development in infants and children, and recommends measures for mitigating SAIGE factor impact in delaying flares and mitigating AD development.

MATERIALS AND METHODS

The project used a modified Delphi process comprising face-to-face expert panel discussions and online follow-up. AA and LS performed systematic literature searches of English-language publications before the panel meeting using PubMed and Google Scholar as secondary sources. Searches addressed SAIGE factors in pediatric AD and the role of cleansing and moisturization using skincare, including ceramide-containing skincare.

The searches encompassed algorithms, clinical studies, consensus papers, guidelines, meta-analyses, and reviews from 2010 to 20 December 2023. Titles, abstracts, and full articles were evaluated for inclusion and categorized according to publication type (Figure 1). The number of clinical studies, including skincare, was insufficient for a clinically meaningful rating.

Role of the Panel

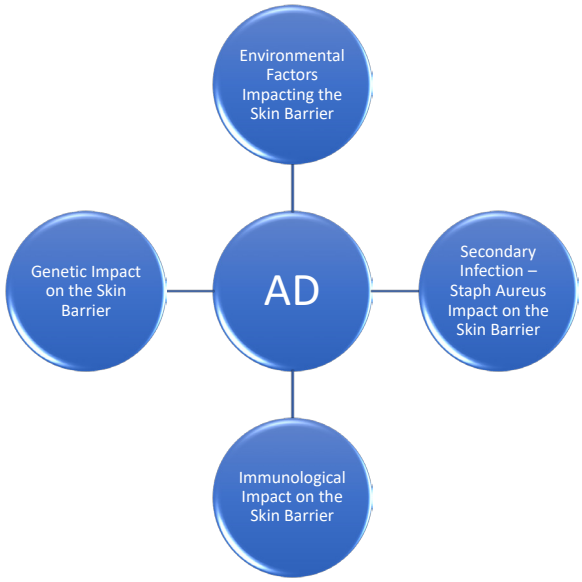
An expert panel of 7 pediatric dermatologists and dermatologists with extensive experience treating pediatric patients convened a meeting on 10 February 2024. They reviewed and discussed the literature to identify four clusters of SAIGE factors impacting the development of AD compromising skin barrier function that may be mitigated by ceramide-containing skincare initiated from birth. The literature search results informed 15 draft statements, and coupled with the panel's opinion and experience, they agreed on 5 statements informing healthcare providers who treat pediatric patients with AD. Consensus ≥80% of the panel [N=7], voting results, statements 1, 3-5: N=7 [100%], statement 2: N=6/7 [88%]).

Statement 1: *S. aureus, Immunological, Genetic, and Environmental (SAIGE) factors play a role in skin barrier dysfunction, a key contributor to AD.*

AD pathophysiology involves a complex interplay between several factors affecting the skin barrier function, including genetic factors, immune dysregulation, skin microbiome imbalance, and environmental factors.[2-4,11-13] The varied AD clinical presentation reflects the complex SAIGE mechanisms underlying the disease (Figure 2).[2-4,11-13] Due to this heterogeneity, AD is increasingly recognized as multifactorial and heterogeneous, with differing phenotypes characterizing different populations.[3,12]

Epidermal barrier dysfunction is a significant AD feature, and genetic, immunological, and environmental factors affect

FIGURE 2. Atopic dermatitis factors that may benefit from skincare.



barrier dysfunction.[2,13,14] Multiple genes involved in immune regulation and epidermal barrier function contribute to AD development, and many cooperating genes are responsible for AD pathogenesis.[4] More than 30 different chromosomal loci with AD susceptibility genes have been reported, and many encode important structural and functional epidermal proteins and innate and acquired immune response regulators.[4] Mutations in epidermal genes impair epidermal barrier function, the most studied of which is filaggrin, a structural protein involved in skin barrier function, and filaggrin-2 mutations are associated with AD persistence.[15] SPINKS, DSG1, and DSP mutations lead to severe epidermal barrier dysfunction and severe AD, whereas TLRs and NLRs mutations cause an immune imbalance in AD.[12,16]

Two different hypotheses for immune dysfunction in AD have been proposed: the inside-out and the outside-in.[2,4] In the outside-in hypothesis, skin barrier dysfunction precedes immune dysregulation and inflammation, and in the inside-out hypothesis, immune dysregulation leads to skin barrier disruption and inflammation. In both models, cytokine-producing T-helper cells and antigen-specific TH2 cells drive immune responses and correlate with AD inflammation and severity.[14,17] Studies show T-cell infiltrates and signaling molecules were observed in lesional and nonlesional skin during AD flares and persisted after months of therapy, indicating continuous immune dysfunction beyond clinically inflamed lesions.[14,17]

Innate and adaptive immunological responses are involved in AD pathophysiology and epidermal barrier dysfunction. Innate immune dysregulation leads to increased infections, decreased tight junction integrity, and defense against *S. aureus* and AD development.[12,16] Adaptive immune dysregulation leads to acute and chronic AD development and chronic lesions in severe AD.[12,16] Controlling these immunological responses using several therapeutic approaches can improve AD outcomes, particularly in genetically predisposed patients.[4,18-20]

Statement 2: *Environmental factors implicated in AD include climate, air pollutants, water, diet and adiposity, and in-utero exposures.*

The complex interplay between genetic AD predisposition and environmental factors contributing to AD pathogenesis is likely driving the dramatic increase in AD morbidity and prevalence.[4,21] The most likely mechanism by which environmental factors impact AD development is through epigenetic changes.[4]

Climate-related risk factors for AD include UV radiation, latitude, and humidity.[22] Studies showed high UV radiation is associated with increased pediatric AD prevalence, whereas increased stratospheric ozone and low UV radiation are related to low AD prevalence.[22] Other studies on climate-related risk factors for AD showed that latitude is inversely correlated with adolescent AD prevalence, and higher outdoor humidity and precipitation are associated with increased AD prevalence.[23]

Environmental exposures such as tobacco smoke, outdoor urban pollution, indoor pollutants, and alkaline water are associated with increased prevalence of AD. Active smoking and tobacco smoke exposure increase genetic polymorphisms and methylation, leading to elevated AD risks in utero, pediatric, and adolescent patients.[21,24] However, one study found no association between infancy AD and maternal smoking during pregnancy.[21] Several studies found that pediatric AD prevalence and severity increased with traffic- and climate-related pollution, including indoor climate in newly built or renovated homes.25 Higher pediatric AD prevalence is associated with alkaline water, and water softeners reduced AD severity in infant, pediatric, and adolescent patients.[26]

In utero exposure to environmental factors, including maternal stress, antibiotic exposure, and alcohol consumption, impacts the risk of infant and pediatric AD development. Several studies show prenatal maternal stress and prenatal antibiotic exposure likely increase pediatric AD risk, while infant antibiotic exposure in the first year of life appeared to be protective.[27] Alcohol exposure during early pregnancy likely increases AD risk; however, studies show discrepancies in whether prenatal alcohol exposure in late pregnancy increases AD risk.[28,29] Over 30 studies found that AD prevalence was increased among children who were overweight or obese compared with children of normal weight.[30] Studies show low maternal vitamin D levels were associated with increased pediatric AD prevalence, and vitamin D supplementation in pediatric patients can improve AD severity.[31,32]

Statement 3: *Increasing evidence shows that S. aureus skin colonization, influenced by multiple factors, plays a pivotal role in the exacerbation and complications of AD.*

Eubiosis of the skin microbiome is important for maintaining a healthy skin barrier and immune response, inhibiting pathogen overgrowth.[11,33,34] Studies show up to 90% of patients with AD are colonized with *S. aureus* in both lesional and nonlesional skin, and the increased *S. aureus* is linked to microbial dysbiosis and reduction of microbiome diversity.[35-38] Although the role of *S. aureus* in AD pathogenesis is not fully established, *S. aureus* overgrowth causes skin barrier dysfunction through virulence factors such as superantigens, enzymes, and other proteins.[35-37] Increasing evidence shows *S. aureus* contributes substantially to AD exacerbation and severity, pruritus, and infectious complications, complicating the management of *S. aureus*-driven AD.[37,39-41] Loss of microbial heterogeneity and *S. aureus* overgrowth occurs during pediatric AD flares.[37,42] Particularly, methicillin-resistant *S. aureus* (MRSA) poses a significant challenge in AD management, and increasingly, patients with AD have MRSA colonization (up to 30%).[37,38] Due to increasing *S. aureus* antibiotic resistance, antibiotic stewardship is essential to preserve the efficacy of AD antibiotics.[43,44]

The risk of developing severe skin infections is increased in pediatric AD patients, likely due to inherited barrier defects.[45] Increased hospitalization is associated with pediatric AD, and hospitalization due to AD flares and related infections is associated with an 8.3-year reduction in lifespan.[46,47] Together, these results show increasing evidence that *S. aureus* colonization is pivotal in AD exacerbation and complications.

Statement 4: *Understanding potentially modifiable environmental risk factors may allow for exposure reduction, which may mitigate and delay AD flares.*

The evidence discussed in statement 2 identifies and establishes environmental factors as contributors to pediatric AD development. Clinical studies show reducing the impact of environmental factors implicated in AD, including climate[22,23], air pollution[25], water[26], diet and obesity[30-32], and in-utero exposures[27,28] decreases AD risk. Recommendations to increase indoor humidity, avoid traffic-related pollution and indoor volatile organic compounds, maintain a healthy diet to reduce obesity, include sufficient vitamin D, and avoid in-utero exposure to stress, antibiotics, tobacco smoke, and alcohol can prevent AD development or reduce severity.[2,4,21] A comprehensive understanding of potentially modifiable environmental risk factors in pediatric AD and strategies to mitigate these is essential for effective AD management and prevention in high-risk populations.[4,12,48]

Several studies have demonstrated the efficacy of ceramide-containing skincare in mitigating SAIGE factor impact by restoring skin barrier function and improving AD outcomes in children and adults.[49,50] One clinical study showed that ceramide-containing moisturizer restored barrier function, making AD-prone skin more resilient to damage, environmental stress, and irritation.[49] Another clinical study showed moisturization reduced AD symptoms and *S. aureus* colonization and improved barrier function, skin hydration, and skin tolerability in adolescents and adults.[50]

Persistent AD is associated with an increased risk of developing atopic comorbidities.[45,51] Mitigating AD in pediatric patients, minimizing or delaying flares might decrease the risk of atopic comorbidities, including extra-cutaneous infections, autoimmune conditions such as vitiligo and alopecia areata, and mental health disorders, particularly attention-deficit hyperactivity disorder, anxiety, and depression.[45,51,52] Pediatric AD may also be associated with lymphoid/hematologic malignancies, obesity, and gastrointestinal immune-mediated disorders.[45,52] Understanding AD comorbidities can potentially improve patient outcomes and help mitigate the QoL impact; clinicians should be aware of strategies to manage comorbidities in a holistic treatment approach.[45,51,52]

Statement 5: *The daily use of moisturizers containing barrier lipids such as ceramides from birth may significantly reduce the incidence of AD in a high-risk population.*

Infant skin develops following birth and is susceptible to barrier dysfunction during maturation.[53] Skincare can bridge the gap between the in-utero protective environment and epidermal barrier development ex-utero, and moisturization is recommended during the neonatal/infancy period.[53,54] Clinical studies evaluating early moisturization in neonates and infants at high risk of AD showed that the cumulative AD incidence was substantially reduced at six months, and most children in the treatment group had normal skin conditions.[55,56] A meta-analysis of 10 clinical studies on the use of skincare in infancy to prevent AD showed a reduction of AD incidence in children at high risk of AD but no significant reduction in AD development in the general population.[57] Furthermore, preventing AD has broader implications in halting the atopic march progression, including the development of food allergy, hay fever, and asthma.[13] Together, these data show that early moisturizer use in infants at high risk of AD can help prevent AD development.[13,53,54]

Although studies on skin care to prevent AD in infants and children have shown positive trends, more recent large-scale studies have failed to confirm these results and showed that AD incidence was similar in treatment and placebo groups.[58]

While Chalmers et al showed the tested emollient failed to reduce AD incidence, other moisturizer formulations may have a different effect, particularly as the tested treatments did not contain ceramides.[13,53,54,58] Another reason for the discrepancies in neonatal skincare study outcomes may be treatment initiation and duration, where studies that found skincare effective in AD prevention in high-risk populations were initiated from birth.[56,57]

Several studies have demonstrated the safety and efficacy of ceramide-containing skincare in restoring skin barrier function and reducing xerosis, pruritus, and AD flares and severity in children and adults.[49,50] Angelova-Fischer et al and Herbert et al showed that the number of AD flares was reduced, and periods of remission between flares were longer with ceramide-containing skincare use.[50,54] A neonatal and infant AD treatment algorithm developed by an expert consensus group recommends ceramide-containing moisturizer as first-line treatment for mild-to-moderate xerosis, erythema (<10% body surface area), and localized erosion.[53] Continuous skincare remains the best approach to improve barrier function, xerosis, and water loss, and is recommended as first-line AD therapy to complement inflammation control.[20,53]

Limitations

We focused on pediatric AD and did not intend to encompass all adult AD aspects, age-related symptoms, and risk factors. Due to limited word count, publications before 2010 were excluded.

CONCLUSION

The panel identified and discussed SAIGE factors that compromise skin barrier function and contribute to AD development in pediatric patients. Recognizing and mitigating SAIGE factors in pediatric patients is particularly important in delaying flares and mitigating AD. Clinician education is needed to improve knowledge of the SAIGE factors' impact on AD and therapeutic strategies, including the continuous use of skincare-containing barrier lipids, such as ceramides initiated from birth, to mitigate AD and delay flare development.

DISCLOSURES

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AUTHOR CORRESPONDENCE

Annake Andriessen PhD

E-mail:..... anneke.a@tiscali.nl