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 ORIGINAL ARTICLE

SAIGE II: The Role of *Staphylococcus aureus* in Skin Barrier Dysfunction and the Development and Severity of Atopic Dermatitis in Young Children

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic inflammatory skin condition that often manifests in infancy or early childhood, with significant impacts on quality of life and potential persistence into adulthood. *Staphylococcus aureus (S. aureus)* colonization and a complex interplay of immunological, genetic, and environmental (SAIGE) factors are key contributors to AD pathogenesis. In pediatric patients, the *S. aureus* colonization induces pruritus, barrier dysfunction, and inflammation, making AD management particularly challenging.

Methods: A panel of 7 pediatric dermatology experts employed a modified Delphi process, including a face-to-face meeting and online follow-up, to evaluate current evidence and formulate consensus recommendations for managing pediatric AD.

Results: The panel identified 6 consensus statements emphasizing *S. aureus* as a critical contributor to pruritus, skin barrier dysfunction, and AD exacerbation, reinforcing the need for effective, early skincare strategies. Recommendations include mitigating SAIGE factors, particularly *S. aureus*, through the proactive use of ceramide-containing skincare from birth in high-risk infants to delay and potentially prevent AD onset.

Conclusions: The consensus panel highlighted *S. aureus* as the most critical SAIGE factor in pediatric AD pathogenesis, driving the itch-scratch-inflammation cycle and contributing to disease exacerbation. Consensus recommendations underscore the role of early, targeted skincare in pediatric AD management to reduce *S. aureus* impact on the skin barrier and support the need for clinician education on SAIGE factors and therapeutic strategies that mitigate AD progression and severity.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition that often emerges in infancy or early childhood, affecting up to 20% of children and potentially continuing into adulthood.[1] It remains uncertain whether AD represents a singular condition or a spectrum of disorders with similar manifestations. The hallmark clinical features of pediatric AD include a relapsing course with eczematous lesions, xerosis, intense pruritus, and a genetic predisposition to atopy.[2]

Despite advancements in both topical and systemic therapies, managing pediatric AD effectively remains challenging, leading to substantial impacts on patients and caregivers.[2] Indeed, annual AD outpatient visits have risen to nearly 2 million, with chronic cases more frequently seen by dermatologists and acute cases, especially in children under 4, more often managed by primary care physicians.[2,3] This underscores the need for enhanced AD treatments and disease management, particularly for pediatric patients, as well as continuous education for pediatric healthcare providers.

The skin microbiome plays a critical role in skin barrier integrity, preventing pathogen colonization and AD occurrence, and modulating immune responses and development in infants.[4,5] Importantly, reduced microbiome diversity is associated with increased *Staphylococcus aureus* (*S. aureus*) colonization in children with AD.[2,5]

S. aureus plays a key role in exacerbating pediatric AD by colonizing the skin, leading to infectious complications such as impetigo, cellulitis, abscesses, and even invasive infections.[6-9] Indeed, increased *S. aureus* colonization is linked to decreased skin microbiome diversity and microbial dysbiosis and affects up to 90% of patients with AD, often both in lesional and nonlesional skin.[5,10,11] *S. aureus* colonization precedes AD onset in children, suggesting a causal role in flares and exacerbation.[6,12] Managing *S. aureus*-driven AD remains problematic, especially infectious complications due to *S. aureus* colonization, including methicillin-resistant *S. aureus* (MRSA).[6,13-15]

AD presents a substantial unmet medical need, as no single therapy currently addresses all AD severities and symptoms across all patient populations, including children.[16,17] Since AD is most prevalent in early childhood, treatments must be both effective and safe for long-term use in infants and children.[1,3] Optimal AD management should encompass several key aspects: controlling inflammation and flare-ups, eliminating xerosis and pruritus, reducing secondary infections, and promoting skin barrier restoration and protection.[18]

This manuscript highlights the 4 interconnected clusters of SAIGE factors (*S. aureus*, immunological, genetic, and environmental) that influence skin barrier function and contribute to AD development in infants and children. Furthermore, the expert consensus panel makes recommendations for strategies to reduce the impact of SAIGE factors, particularly *S. aureus*, by delaying flares and mitigating pediatric AD progression.

MATERIALS AND METHODS

This 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. The searches addressed SAIGE factors in pediatric AD, focusing on the role of *S. aureus*.

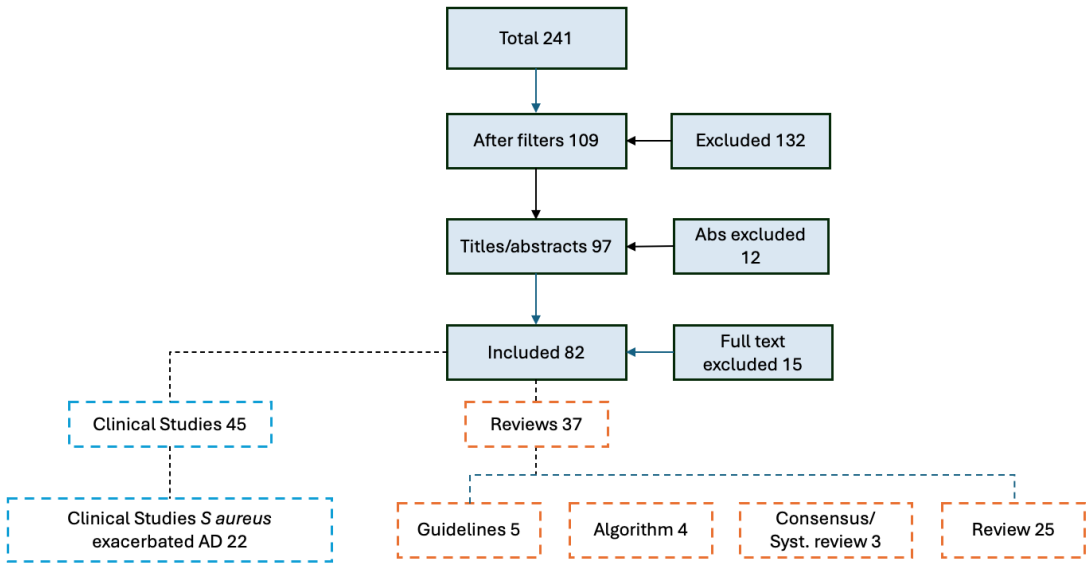
Searches

The searches encompassed clinical studies, algorithms, consensus papers, guidelines, meta-analyses, review papers, and systematic reviews from 2010 to June 20, 2024. The literature search was based on 2 key questions:

1. WHAT IS KNOWN ABOUT AD development in neonates, infants, and children influenced by SAIGE factors focusing on *S. aureus-driven exacerbation* of AD compromising skin barrier function?
2. WHAT IS THE ROLE OF SKIN CARE and ceramides-containing skincare from birth in addressing SAIGE factors, focusing on *S. aureus* attenuating pediatric AD and promoting a healthy skin barrier?

Abstracts and then full articles were evaluated for inclusion and categorized according to publication type (Figure 1). Each clinical publication that included skincare was graded based on reviewer consensus, and any discrepancies were resolved by discussion. The reviewers assigned a level of evidence

FIGURE 1. Results of the literature searches on topical treatment of AD and *S. aureus* exacerbated AD.



Excluded: Publication language other than English, not including pediatric patients, topical treatment, or *S. aureus* exacerbated AD/impetigo.

for each treatment (levels A, B, C, and 1 to level 4) using the pre-established criteria. Publications in a language other than English, not including pediatric patients, topical treatment, or *S. aureus* exacerbated AD/impetigo, were excluded.

Role of the Panel

An expert panel of 7 pediatric dermatologists with extensive experience treating pediatric patients convened at a meeting on July 11, 2024. They reviewed and discussed the literature to identify the role of *S. aureus*, 1 of the SAIGE factors impacting the development of AD, compromising skin barrier function that may be mitigated by ceramide-containing skincare initiated from birth.

During the meeting, advisors divided into 3 groups. The systematic literature search results informed 13 draft statements, and coupled with the panel's opinion and experience, they agreed (consensus ≥80% of the panel) on 6 statements supporting healthcare providers who treat pediatric patients with AD. The statement voting results were statements 1 to 4: N=7 [100%] and statements 5, 6: N=6/7 [88%].

RESULTS

Statement 1: *The common description of AD as "an itch that rashes" reflects the observation that pruritus may be observed before apparent signs of skin inflammation in many patients. Pruritus is an important element in AD disease progression.*

Clinical features highly characteristic of AD include a relapsing course with eczematous lesions, intense pruritus, xerosis, and a genetic predisposition to atopy.[2] Pruritus remains a substantial burden in patients with AD, with a considerable impact on quality of life (QoL) and social withdrawal.[2,19,20] Indeed, over 60% of patients with moderate-to-severe AD report severe or unbearable pruritus, and 55% experience inadequate disease control.[20]

Furthermore, pruritus is not only a burdensome AD symptom but is a key factor in AD pathogenesis and progression.[9,19] A prevailing AD paradigm has been that inflammation could be either the cause or the result of pruritus.[19] However, recent evidence has shown that *S. aureus* plays a key role in the itch-scratch-inflammation cycle and that *S. aureus*-driven pruritus leads to inflammation.[9] Indeed, topical *S. aureus* application induced robust scratching in mice and exacerbated skin damage akin to human AD, underscoring the importance of surface colonization in driving itch and skin damage.[9]

Furthermore, *S. aureus* colonization causes pruritus, skin damage, and inflammation through toxins and protease production that induce the host protease-activated receptor 1 (PAR1) signaling pathway. Through quorum sensing in dense skin colonies, S. aureus secretes autoinducing peptides, which lead to the upregulation of protease, V8, and phenol-soluble modulin (PSM) toxins. Upregulated V8 and PSMs then activate the PAR1 signaling pathway in pruriceptor nerves, triggering pruritus. Indeed, systematic mutation studies attribute itch occurrences to V8 upregulation in mouse skin and in samples of human lesional AD skin. Furthermore, V8 skin injections induced robust itch and drove skin damage in mice. *S. aureus* secreted V8 activates PAR1 signaling, leading to pruritus and scratching, which damages the epidermal barrier, causes inflammation, and further facilitates *S. aureus* growth.[9]

Evidence showing that anti-IL-4Ra therapy reduces *S. aureus* colonization and relieves pruritus further supports the causative role of *S. aureus* in the itch-scratch-inflammation cycle.[19] Patients report that pruritus improves within days of initiating anti-IL-4Ra therapy, preceding improvements in skin lesions by weeks. Overall, these findings support the paradigm that AD is 'the itch that rashes', with pruritus often preceding visible AD signs in many patients.

Statement 2: *S. aureus, 1 of 4 SAIGE factors (S. aureus, Immunological, Genetic, and Environmental), impacts AD development in newborns, infants, and children.*

The Role of SAIGE Factors in AD

AD pathogenesis involves a complex interplay of SAIGE factors (*S. aureus*, immunological, genetic, and environmental), with *S. aureus* colonization critical to skin barrier dysfunction.[17,18,21-24] This *S. aureus*-driven barrier impairment is particularly important in initiating infantile AD.[25] The diverse AD clinical presentation reflects the complex interactions among SAIGE factors central to AD etiology.[18,21-24] Due to this heterogeneity, AD is increasingly regarded as a spectrum of disorders with shared clinical features.[21,22]

Multiple susceptibility genes involved in epithelial barrier function and immune regulation contribute to AD development and pathogenesis.[24] Mutations in functional epidermal proteins, particularly the structural protein filaggrin, impair barrier function and are associated with AD persistence.[6,26]

AD pathophysiology and epidermal barrier degradation involve dysregulation of both innate and adaptive immune responses. Dysregulation in these immune pathways leads to increased susceptibility to infections, decreased tight junction integrity, and impaired defense against *S. aureus* in chronic lesions.[22] These immunological alterations are particularly evident in developing and severe AD.

Environmental factors such as climate, air pollution, water quality, diet, adiposity, and prenatal exposures are also implicated in AD. These environmental factors most likely influence AD development through epigenetic modifications.[24] The intricate interaction between environmental and genetic factors not only contributes to AD onset and severity but likely also drives the dramatic increase in AD prevalence and morbidity.[24]

S. aureus Colonization on AD Skin

Skin microbiome homeostasis is critical for maintaining epidermal barrier function, immune regulation, and pathogen resistance.[4,5,23] However, *S. aureus* abundance in AD is closely associated with microbial dysbiosis and reduced microbiome diversity.[6,10,11,13] Indeed, research shows *S. aureus* colonizes both lesional and nonlesional skin in 60 to 100% of patients with AD compared to only 5 to 30% of healthy individuals.[6,13] In addition, AD severity is correlated with greater *S. aureus* abundance.[9,20] Mounting evidence suggests *S. aureus* colonization plays a causative role in epidermal barrier disruption, AD development, exacerbation, impetiginization, and infectious complications.[6-9,17] Notably, *S. aureus* colonization precedes AD development, with overgrowth and skin dysbiosis observed during pediatric AD flares.[6,9,17] Moreover, hospitalization due to AD flares and related infections is estimated to reduce lifespan by 8.3 years.[27] This increasing evidence underscores that *S. aureus* colonization is a key contributor to AD development, exacerbation, and risk of infectious complications.

S. aureus-driven impetiginization and infectious complications present major challenges in AD management, particularly with the increased risk of methicillin-resistant *S. aureus* (MRSA) invasive infections.[6,7] Pediatric patients with AD are especially vulnerable to impetiginization and infectious complications, likely due to underdeveloped stratum corneum (SC) in infants and young children.[16] Studies show that MRSA prevalence is rising, with MRSA colonizing up to 30% of patients with AD.[6,13,15] Moreover, MRSA-colonized AD skin exhibits further reduced skin barrier integrity and microbiome diversity compared to methicillin-sensitive *S. aureus* (MSSA)-colonized AD skin.[6,7,13]This exacerbates AD severity and elevates the rates of invasive infections in patients with MRSA.[6] Importantly, the increasing antibiotic resistance of MRSA in AD complicates antibiotic treatment and heightens the risk of MRSA infectious complications.[6,13,15] Consequently, the growing *S. aureus* resistance emphasizes the importance of antibiotic stewardship to maintain AD antibiotic efficacy.[6,7,28]

Statement 3: *S. aureus colonization on AD skin is associated with multiple physiological dysfunctions that may exacerbate AD. These include:*

- *Strength of S. aureus-corneocyte adhesion*
- *Release of proteases*
- *Deficiency of antimicrobial peptides*
- *Decreased levels of filaggrin and filaggrin degradation products*
- *Overexpressed Th2/Th17 cytokines*
- *Altered microbiome*
- *Altered lipid profiles*

Association Between *S. aureus* Colonization and Physiological Dysfunctions

While the precise role of *S. aureus* in AD pathogenesis remains unclear, its overgrowth contributes to skin barrier dysfunction through virulence factors, including superantigens, enzymes, and other proteins.[6,10,11] Several risk factors predispose to *S. aureus* colonization, such as *S. aureus*-corneocyte adhesion strength, antimicrobial peptide deficiency, reduced filaggrin and its breakdown products, elevated Th2/Th17 cytokines, altered lipid profiles, and microbial dysbiosis (Figure 2).[6,11,26,29-35]

S. aureus-corneocyte adhesion contributes to *S. aureus* colonization, and the binding strength is regulated by the natural moisturizing factor.[33] Reduced levels of natural moisturizing factor in the SC are associated with increased AD severity (Figure 2). Research shows that *S. aureus* adhesion is significantly stronger to corneocytes with reduced natural moisturizing factor levels.[33] Notably, mechanical tension dramatically strengthens *S. aureus*-corneocyte adhesion, demonstrating that physical stress, such as scratching, promotes *S. aureus* colonization on AD skin.[33]

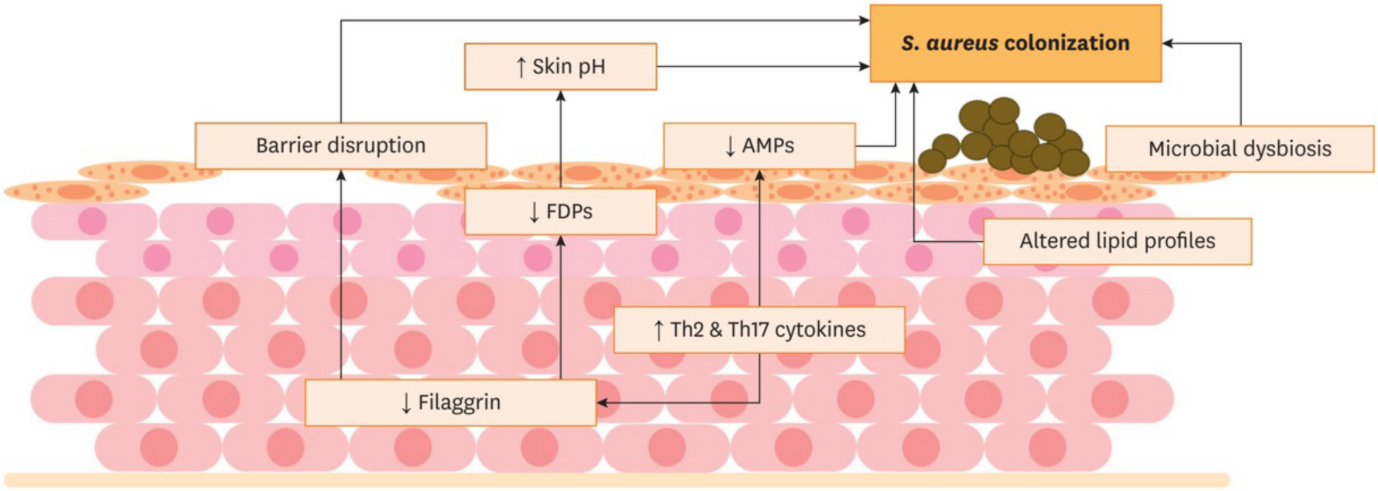
S. aureus production of protease V8 causes pruritus and scratching, which damage the epidermal barrier, cause inflammation, and further facilitate *S. aureus* colonization.[9] Evidence shows V8 upregulation in high-density *S. aureus* activates the PAR1 signaling pathway in pruriceptor nerves, leading to an itch-scratch cycle and driving skin damage.[9]

Studies show that *S. aureus* colonization is increased in patients with AD and filaggrin gene mutations.[30] Filaggrin and filaggrin degradation products, such as urocanic acid and pyrrolidone carboxylic acid, are natural moisturizing factors that maintain skin pH and prevent *S. aureus* colonization (Figure 2).[26,30]

S. aureus directly impairs skin barrier function and upregulates proinflammatory Th2/Th17 cytokines, leading to AD inflammation and exacerbation (Figure 2).[36] Furthermore, overexpressed Th2 cytokine substantially alters the lipid composition in the SC in AD skin (Figure 2).[32] SC lipids, such as ceramides, free fatty acids, and sphingosine, maintain skin barrier integrity and prevent *S. aureus* colonization.[35] Hence, aberrant lipid profiles can exacerbate *S. aureus* colonization on AD skin.[32]

Commensal bacteria on healthy skin prevent *S. aureus* colonization and AD inflammation by producing antimicrobial peptides.[11,29,31] However, evidence shows that AD skin is deficient in antimicrobial peptides, including cathelicidin and human beta-defensin, which enables chronic *S. aureus* colonization (Figure 2).[29,31]

FIGURE 2. Factors contributing to *Staphylococcus aureus* colonization on atopic dermatitis skin.



Physiological dysfunctions that contribute to *S. aureus* colonization include: *S. aureus*-corneocyte adhesion strength, antimicrobial peptide deficiency, reduced filaggrin and its breakdown products, elevated Th2/Th17 cytokines, altered lipid profiles, and microbial dysbiosis.[6] AD, atopic dermatitis; FDP, filaggrin degradation product; AMP, antimicrobial peptide.

S. aureus-Driven Physiological Dysfunctions Exacerbate AD

Increased *S. aureus* abundance and decreased skin microbiome diversity precede and cause AD flares and exacerbation.[5,6,9,12] Studies show increased *S. aureus* abundance during untreated AD flares and reduced microbiome diversity during intermittent and post-treatment flares.[5,36] Furthermore, lack of AD flare treatment leads to vicious cycles between *S. aureus* colonization and AD exacerbation.[5,36] Recent evidence has shown that *S. aureus* is a key driver in the itch-scratch-inflammation cycle, which further facilitates *S. aureus* growth and AD exacerbation.[9]

Thus, the causal role of *S. aureus* in AD severity and exacerbation is well-established.[5,6,9,12] Hence, physiological dysfunctions that contribute to *S. aureus* colonization, such as *S. aureus*-corneocyte adhesion strength, antimicrobial peptide deficiency, reduced filaggrin and its breakdown products, elevated Th2/Th17 cytokines, altered lipid profiles, and microbial dysbiosis, also facilitate AD exacerbation.[6,11,26,29-35]

Statement 4: *In addition to triggering pruritus, S. aureus toxins have been postulated to contribute to keratinocyte apoptosis and skin barrier defects, exacerbating AD.*

S. aureus produces superantigens and toxins that play a role in keratinocyte apoptosis and skin barrier defects.[6,10,11] Indeed, research shows that *S. aureus* colonizes approximately 90%of patients with AD, with 50 to 60% of these strains producing toxins.[37] Through quorum sensing in dense skin colonies, *S. aureus* secretes autoinducing peptides, which lead to the upregulation of toxins and proteases that activate the PAR1 signaling pathway in the preceptor's nerves and trigger pruritus.[9] Specifically, *S. aureus* overexpresses protease V8, α-toxin, PSM toxins, and protein A, which affect keratinocytes and stimulate proinflammatory responses.[9,34]

S. aureus expresses complex patterns of superantigens, including staphylococcal enterotoxin A, B, C, and D, as well as toxic shock syndrome toxin 1.[37] These superantigens activate polyclonal T cells and induce T cell-mediated inflammation in AD lesions.[34] Notably, staphylococcal enterotoxin B induces IL-31 upregulation, which inhibits keratinocyte differentiation and suppresses filaggrin expression.[34]

This evidence shows that the *S. aureus* superantigens, toxins, and proteases induce keratinocyte apoptosis and inflammatory responses, leading to pruritus and inflammation.[9,19] Both keratinocyte apoptosis and pruritus-induced scratching compromise the skin barrier. Furthermore, growing evidence shows that this *S. aureus*-driven skin barrier dysfunction facilitates pathogen growth and plays a critical role in infectious complications such as impetigo, cellulitis, abscesses, and invasive infections.[7,8] These data support the paradigm that *S. aureus* damages the skin barrier and exacerbates AD inflammation through the release of superantigens, toxins, and proteases that affect keratinocytes and induce inflammatory responses.

Statement 5: *Early daily use of moisturizers has been shown to reduce or delay the onset of AD.*

S. aureus colonizes both lesional and nonlesional skin in the majority of patients with AD, compromising the skin barrier even in unaffected AD skin.[6,13,15] Consequently, reducing *S. aureus* colonization and restoring the microbiome and the skin barrier are essential to resolve AD flares and control chronic disease.[17,36] Given the chronic nature of AD, ongoing care is required to maintain the skin barrier and prevent future exacerbations, even in the absence of active disease. Indeed, studies show early and consistent emollient use from birth can reduce or delay AD onset in high-risk populations.[28]

Infant SC develops postnatally and is vulnerable to barrier disruption and impetiginization during maturation.[16] Skincare is important between the protective in-utero environment and ex-utero epidermal barrier development, hence moisturization is recommended for neonates and infants.[28] Indeed, several clinical studies have demonstrated that early moisturization in neonates and infants substantially reduces AD incidence in children at high risk of AD, but no significant reduction was observed in the general population.[38,39] Additionally, evidence shows that preventative treatment to reduce *S. aureus* colonization and restore the skin barrier in pediatric patients with AD results in improved microbiome diversity.[17] Since current AD therapies are not curative, such preventative treatment may improve long-term outcomes and potentially halt atopic march progression.[28] Overall, the data suggest that early skincare initiated from birth can delay or prevent AD development in infants at high risk.

Statement 6: *Skincare with a ceramide-containing moisturizer cream has been shown to reduce barrier dysfunction, pruritus, and redness and improve clinical outcomes and quality of life associated with AD.*

The evidence discussed above underscores the importance of controlling *S. aureus* colonization and resulting pruritus and restoring skin barrier integrity in effective AD management. Skincare can decrease *S. aureus* colonization and pruritus and improve skin barrier function and AD severity.[28,35,40,41] Indeed, multiple studies have demonstrated the safety and efficacy of ceramide-containing skincare in restoring skin barrier function and reducing pruritus, AD flares, and severity in children and adults.[38,39,42] A clinical study showed that ceramide-containing skincare reduced *S. aureus* colonization and improved the skin barrier (hydration), AD severity, pruritus, and prolonged remission periods between flares in children and adults.[42] Another clinical study showed that ceramide-containing skincare reduced AD incidence and extended remission periods between flares in infants.[39]

Consequently, a neonatal and infant AD treatment algorithm developed by an expert consensus group recommends ceramide-containing skincare as prevention and first-line treatment for mild-to-moderate pediatric AD.[28] Thus, skincare remains the only approach to simultaneously improving barrier function, pruritus, and AD severity. It is recommended as AD prevention and treatment to complement inflammation control.[28,35,40,41]

While several studies on preventative AD skincare in infants and children have shown positive trends, a recent large-scale study reported similar AD incidence in treatment and placebo groups.[43] However, the tested emollient lacked ceramides, which may have impacted its effectiveness.[38,39] These discrepancies in neonatal skincare outcomes could also be attributed to variations in treatment timing and duration, with studies showing the efficacy of continuous skincare initiated from birth.[38] Overall, these findings underscore the importance of moisturizer composition and skincare timing and duration, with continuous ceramide-containing skincare initiated from birth showing the most benefit.

DISCUSSION

AD presents an unmet clinical need for a single topical AD therapy that effectively reduces *S. aureus* colonization and pruritus and restores skin barrier function to improve AD severity in both pediatric and adult patients.[16,40,41] The consensus panel highlighted *S. aureus* as the most critical SAIGE factor in AD management, supporting the paradigm that AD is "the itch that rashes". The panels' clinical observations are improved AD outcomes with early mitigation of *S. aureus* colonization using skincare. The panel agreed that their clinical observations correlated well with recent data showing *S. aureus* drives the itch-scratch-inflammation cycle.[9] Furthermore, the panel noted that AD ceramide-containing skincare may decrease the atopic march and mitigate antibiotic overuse. Additionally, the relationship between *S. aureus* and ceramides may be bidirectional, and further research is needed on the effect of *S. aureus* secreted proteases on ceramides.

CONCLUSION

Addressing *S. aureus* colonization can reduce pruritus, restore the skin barrier, and prevent secondary infections, which are all critical in managing AD exacerbation and progression. Emerging evidence supports that early, consistent skincare, especially using ceramide-containing moisturizers, can reduce or delay AD onset in high-risk infants and mitigate AD exacerbations and complications in young children. *S. aureus*-related mechanisms and their interaction with other SAIGE factors will be necessary to establish comprehensive AD skincare strategies, improve long-term outcomes, and enhance the quality of life for pediatric patients with AD.

DISCLOSURES

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