doi:10.36849/JDD.9230

 ORIGINAL ARTICLE

The Atopic Dermatitis Continuum: An Updated Paradigm for a Common Disorder and a Novel Multipurpose Treatment Option

Lawrence A. Schachner MD FAAD FAAP,[a] Adelaide A. Hebert MD FAAD,[b] Nanette Silverberg MD FAAD FAAP,[c] Anneke Andriessen PhD,[d] Pearl C. Kwong MD FAAD FAAP,[e] Mercedes E. Gonzalez MD FAAD,[f] Dennis P. West PhD FCCP,[g] Peter Lio MD FAAD[h]

[a]Dermatology and Pediatrics, Pediatric Dermatology, University of Miami School of Medicine, Miami, FL
[b]Department of Dermatology and Pediatrics, McGovern Medical School, and Children's Memorial Hermann Hospital, Houston, TX
[c]Department of Pediatric and Adolescent Dermatology, St Luke 's-Rosevelt and Beth Israel Medical Centers, NY, NY
[d]Radboud UMC Nijmegen, Andriessen Consultants, Malden, The Netherlands
[e]Wolfson Children's Hospital, Jacksonville, FL
[f]Pediatric Skin Research, Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL
[g]Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL
[h]Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL

ABSTRACT

Background: Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder characterized by complex interactions among *Staphylococcus aureus* colonization and immunologic, genetic, and environmental (SAIGE) triggers. Currently, no single therapy comprehensively addresses all triggers and the full spectrum of AD manifestations, highlighting an unmet need for therapies that simultaneously target all components of the disease continuum.

Methods: An expert panel conducted a structured literature review and developed consensus statements during a meeting in March 2025.

Results: The consensus highlighted the triggers and continuum of four interdependent pathological presentations perpetuating disease progression: inflammation, colonization/dysbiosis/infection, xerosis, and pruritus - termed the "four demons".

In a phase 2a clinical trial, topical zabalafin hydrogel was shown to reduce inflammation, skin dysbiosis, *Staphylococcus aureus* colonization/infection, reduce pruritus, and xerosis with minimal adverse effects in patients with mild to moderate AD.

Conclusions: Recognizing AD as a Continuum emphasizes the necessity for multi-targeted therapeutic strategies. By addressing the interconnected processes of inflammation, infection, pruritus, and xerosis within the AD Continuum, zabalafin offers a promising therapeutic option for sustained disease control.

J Drugs Dermatol. 2025;24(9):920-927. doi:10.36849/JDD.9230

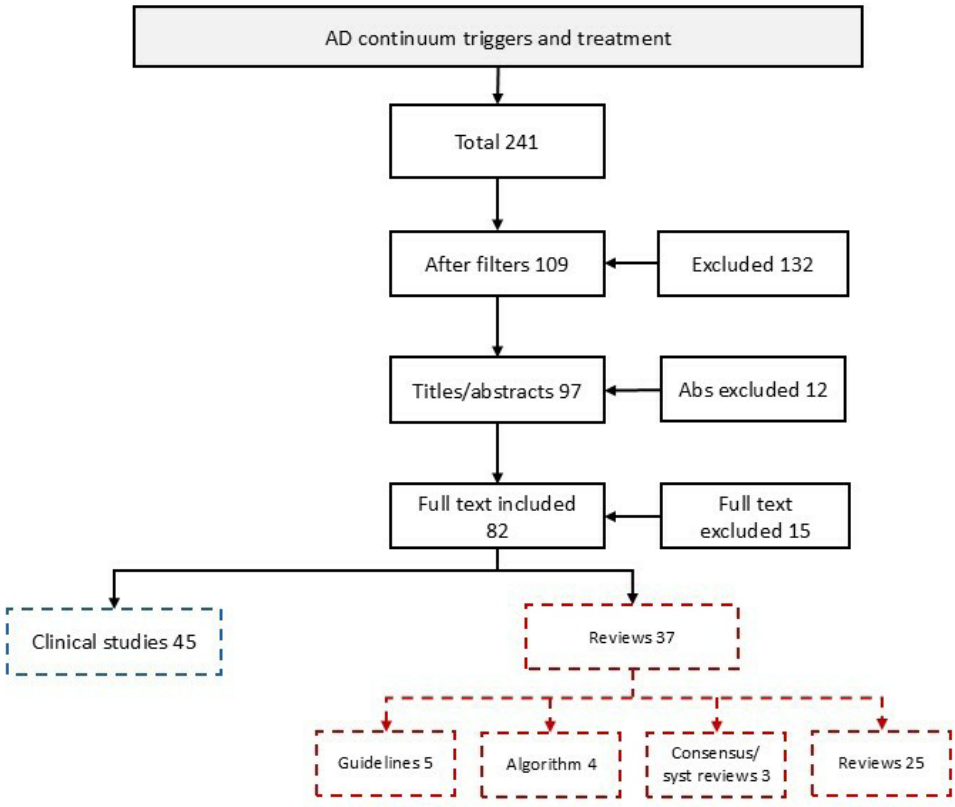
INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder that typically begins in infancy or early childhood, affecting up to 20% of children and 10% of adults globally, with significant variability in clinical presentation and disease severity.[1] The disease is characterized by a cycle of interdependent pathological presentations, inflammation, skin dysbiosis predominantly involving *Staphylococcus aureus* (*S. aureus*) and subsequent infection, intense pruritus, and xerosis.[1,2] These features, termed the "four demons," perpetuate and exacerbate one another along an AD Continuum, complicating effective disease management and profoundly affecting quality of life.[2-4]

The pathogenesis of AD is multifactorial, driven by complex interactions among various SAIGE triggers: *S. aureus* colonization/infection, immune dysregulation, genetic predisposition, and environmental influences.[5,6] Evidence suggests that these SAIGE factors contribute to both disease exacerbation and onset, with *S. aureus* colonization preceding clinical manifestations and driving inflammation as well as directly inducing pruritus through neuroimmune interactions.[7-9]

Despite advances in AD therapies, current treatments do not comprehensively address the entire AD Continuum and the underlying SAIGE triggers.[10-12] Limitations in management strategies, combined with the complexity of AD and its

FIGURE 1. Structured literature searches.



Search terms:
AD triggers AND skin dysbiosis OR *Staphylococcus aureus*-driven colonization OR infection OR immunological OR genetic OR environmental OR inflammation.AD flares AND topical treatment OR topical corticosteroids OR topical calcineurin inhibitors OR PDE-4 I OR Zabalafin OR topical antimicrobial OR antimicrobial resistance OR topical antibiotic OR topical antibiotic resistance OR bleach baths OR systemic treatments OR biologics OR JAK inhibitors. Excluded: Publication language other than English

management, underscore the need for comprehensive therapeutic approaches to management that directly and simultaneously address the four demons of AD to achieve sustained disease control.[6,13] Notably, the multi-targeted zabalafin botanical hydrogel addresses all aspects of the AD Continuum, bridging existing therapeutic gaps in AD management.[14]

MATERIALS AND METHODS

Role of the Expert Panel

A panel (advisors) of seven experts in dermatology, including board-certified dermatologists and pediatric dermatologists, gathered for a face-to-face meeting on March 5, 2025, in Orlando, Florida. The advisors discussed the results of a literature review and, coupled with their clinical knowledge and experience, developed consensus statements for AD management. An online review was conducted to refine the statements and provide clear guidance on treating and maintaining control of the AD Continuum, highlighting the properties of zabalafin botanical hydrogel.

Literature Review

AA conducted a structured literature review on AD triggers and current best practices in topical AD treatment, searching PubMed and Google Scholar on February 4 and 5, 2025, with the search terms listed in Figure 1. The review process involved examining titles and abstracts, followed by full articles. Selected articles included clinical guidelines, algorithms, consensus papers, systematic literature reviews, clinical studies, and reviews published in English from January 2015 to January 2025. Publications in languages other than English and those deemed not clinically relevant to AD triggers and treatments were excluded. Selected publications were manually reviewed and graded based on the level of evidence and reviewer consensus, with any discrepancies resolved through discussion. This process yielded 82 articles that qualified for inclusion and were deemed clinically relevant to inform an updated paradigm for AD and topical AD treatment. These publications comprised 45 clinical studies and 37 reviews (Figure 1).

RESULTS

Statement 1: *AD exists and evolves along a Continuum that features four major skin findings: inflammation, dysbiosis/colonization/infection, pruritus, and xerosis, the so-called four demons.*

Among skin disorders, AD has the highest global disease burden, resulting in an 8.3-year reduction in lifespan and $250 million in healthcare costs in the US.[15] This highlights an unmet need for more cost-effective and personalized long-term treatment strategies that balance efficacy with affordability and address all aspects of AD.[5,6]

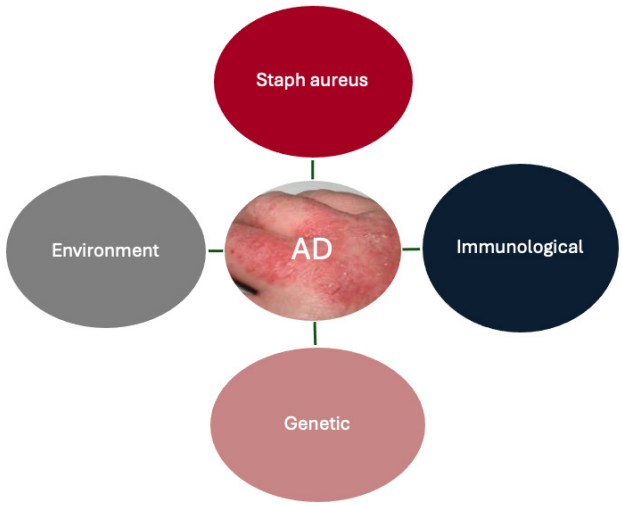
AD has a relapsing course characterized by flares associated with four interdependent pathological presentations, the four demons.[2] These clinical manifestations coexist across different disease stages, perpetuating and exacerbating AD. Emerging evidence indicates that these elements are not isolated phenomena but interconnected components of a unified AD Continuum. For instance, pruritus is a burdensome AD symptom and a key factor in its pathogenesis and progression, as inflammation leads to pruritus, scratching, skin damage, and *S. aureus*-driven infection.[14] Skin microbiome dysbiosis facilitates inflammation, *S. aureus*-driven colonization, infection, pruritus, and xerosis.[1,3,7,8] *S. aureus*-driven dysbiosis often precedes AD development, and pathogenic colonization and infection may be observed during AD flares, indicating a causal role in AD flares and exacerbations.[1,3,7,8,16] In turn, xerosis arises from inflammation-mediated barrier disruption and contributes to barrier degradation, facilitating infection and creating a perpetuating cycle that sustains inflammation.[3] This perpetuating cycle characterizes AD as 'the itch that rashes,' with pruritus and pathogen colonization/infection frequently preceding visible inflammation.[8,16] AD is characterized by the four demons, which evolve along the AD Continuum that perpetuates and exacerbates AD (Figure 2).

FIGURE 2. The four demons of the atopic dermatitis pendulum-wise continuum.

Adapted with kind permission from Schachner et al[5] RBC consultants

Statement 2: *AD has multiple triggers, which can be grouped into SAIGE [S. aureus, Immune, Genetic, Environmental] categories.*

FIGURE 3. *Staphylococcus aureus*, immunological, genetic, and environmental (SAIGE) triggers of atopic dermatitis.[5]



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AD is influenced by various triggers involving complex interactions among SAIGE factors (Figure 3).[5,13] The diverse AD clinical presentations reflect these complex SAIGE mechanisms central to AD etiology.[5,13] Immune dysregulation is a core aspect of AD pathophysiology. AD development and progression involve dysregulation of innate and adaptive immune responses, leading to decreased epidermal integrity and increased susceptibility to *S. aureus* colonization/infection.[16,17] For example, immune cells such as the helper cells, basophils, macrophages, and inflammatory cytokines (eg, thymic stromal lymphopoietin, interleukins, and alarmins) drive immune responses and pruritus in AD.[16,17] Importantly, infiltrating immune cells, signaling molecules, and skin barrier dysfunction were observed in lesional and nonlesional AD skin during flares, persisting beyond treatment.[16,17]

Immunological factors contribute to AD by impacting epidermal barrier degradation. Activated T-helper and their specific cytokines upregulate KLK7, while downregulating FLG and lipid organization, impacting keratinocyte activity and causing barrier dysfunction.[17] This suggests continuous immune dysfunction drives skin barrier degradation, AD progression, and severity.

Genetic predisposition also significantly contributes to AD susceptibility. Multiple genes involved in epithelial barrier function and immune regulation confer susceptibility to AD development and contribute to its progression.[16,17] Mutations in functional epidermal proteins, such as filaggrin, cause barrier dysfunction and are associated with AD persistence.[16]

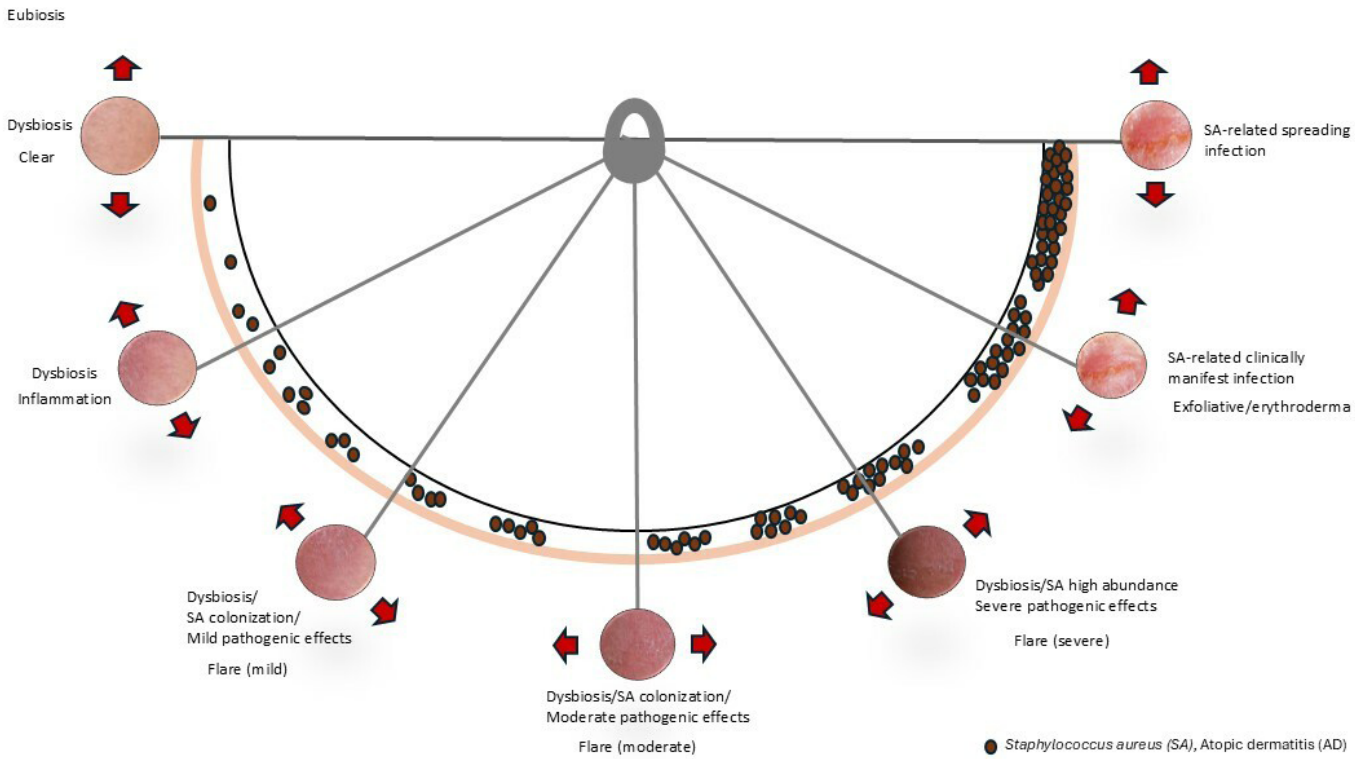
Environmental factors, including climate, allergens, air pollution, water quality, diet, adiposity, and prenatal exposures, are also implicated in AD prevalence and severity.[5] The complex interaction between environmental and genetic factors not only contributes to AD onset and severity but likely also drives increases in AD prevalence and morbidity.[5] These insights substantiate that the multifactorial nature of AD involves interconnected SAIGE triggers.[5]

Statement 3: *Increased S. aureus and decreased skin microbiome diversity precede and contribute to AD severity, flares, and exacerbation. Consistent AD treatment over time, including skincare, is required to reduce S. aureus colonization and restore microbiome diversity.*

Increased *S. aureus* colonization and decreased skin microbiome diversity precede AD flares and contribute to disease severity and exacerbation.[1,7,9] Studies show that up to 90% of patients with AD are colonized with *S. aureus* in lesional and nonlesional skin, and colonization occurs prior to AD flares, suggesting a critical role in disease onset.[1,7] Patients with *S. aureus*-related AD frequently present with distinct clinical phenotypes characterized by inflammation, increased disease severity, and more frequent exacerbations.[3,7,9] The role of *S. aureus* in AD extends beyond colonization, with evidence suggesting a continuum between dysbiosis, colonization, and infection, where increasing *S. aureus* abundance correlates with escalating disease progression.[6,9,13] Initially, mild dysbiosis can result in mild inflammation or flares, progressing through *S. aureus* overabundance associated with moderate to severe AD flares. *S. aureus* colonization may progress to clinically manifest infections, such as cellulitis or furunculosis. This continuum illustrates how *S. aureus* plays a prominent and exacerbating role in AD progression and how its abundance significantly impacts clinical outcomes.[6,7] Therefore, the advisors emphasize the need to recognize *S. aureus* not as a separate indication for treatment when infection occurs but as part of a disease continuum that includes a subset of infected patients. In the *S. aureus*-driven AD Continuum, the predominant colonizing *S. aureus* mutates into a pathogenic variant, leading to AD exacerbation and, ultimately, clinical manifestation of infection.[18] As pathogenic *S. aureus* is reduced through treatment, an apoptotic signal mediated by quorum sensing leads to pathogenic *S. aureus* death, allowing the predominant *S. aureus* to revert to the initially colonizing strain.[18]

Other SAIGE factors impact the *S. aureus*-driven AD Continuum pendulum in either direction (Figure 4).[5,13] Patients with *S. aureus*-associated AD flares exhibit greater type 2 immune deviation, allergen sensitization, and epidermal barrier disruption.[3,9,13]

FIGURE 4. The Schachner Pendulum: *Staphylococcus aureus*, immunological, genetic, and environmental (SAIGE) triggers of atopic dermatitis.[5]



Pathogenic effects of SA on AD: SA expresses superantigens (eg, SE and TSST-1) that activate basophils, causing T-cell-mediated inflammation. PSMα and PSMβ stimulate the release of proinflammatory cytokines from keratinocytes. Protein A and lipoproteins of SA trigger proinflammatory responses by activating TNFR-1 and TLR2 on keratinocytes. Staphylococcal enterotoxin (SE), toxic shock syndrome toxin-1 (TSST-1), Phenol-soluble modulins (PSM), Tumor necrosis factor receptor-1 (TNFR-1). The Schachner Pendulum was adapted with kind permission of Dr Schachner et al[5] and RBC consultants.

Colonizing *S. aureus* invades atopic skin, releasing toxins that stimulate the inflammatory cascade. *S. aureus* expresses several molecules that contribute to AD by interacting with immunological factors.[3] Studies show that untreated AD flares exhibit higher *S. aureus* abundance and reduced microbiome diversity compared to intermittent and post-treatment flares.[1,7] The absence of AD flare treatment creates a vicious cycle of *S. aureus* colonization and AD exacerbation.[1,4] This highlights the clinical need for a comprehensive AD treatment that addresses dysbiosis and *S. aureus* overabundance, which progresses to infection while restoring skin barrier function.[1,6]

Statement 4: *No single product is currently effective against the full spectrum of AD manifestations.*

No single therapeutic product effectively addresses the entire Continuum of AD manifestations (Table 1).[5,6] No single antibiotic is suitable for all infected AD severities or effective against all *S. aureus* strains. Clinical practice guidelines reflect this, recommending combinations of numerous therapeutics in an escalated approach, ranging from topical treatments to systemic therapies based on AD severity, relapse, and patient age.[10-12] In conventional treatment approaches, infection is typically regarded as a distinct condition that needs to be resolved separately. Most conventional AD treatments do not address critical factors such as dysbiosis and *S. aureus* colonization, necessitating supplementary topical interventions.[5,6] Instead, AD management focuses on controlling inflammation and pruritus with therapies often associated with significant adverse effects that limit long-term continuous use.[10-12] A critical aspect of AD management is preventing AD flares, particularly those with signs of secondary infection, which often require treatment escalation.[4] If untreated, bacterial infections may become invasive or systemic.

Clinical practice guidelines strongly recommend skincare with emollients for mild AD and as an adjunctive therapy for moderate to severe AD. Beyond emollients, topical treatments, including TCS and TCI, remain the cornerstone for managing mild-to-moderate AD by primarily reducing inflammation. Topical corticosteroid potency can be tailored to lesion location and thickness, with potent agents like clobetasol propionate

TABLE 1.

Zabalafin Multi-Targeted Treatment Addresses the Total Atopic Dermatitis Continuum

Atopic Dermatitis	Targets Immune Component		Targets Bacteria Staph & MRSA		Reduces		Long Term
Treatment	Itch	Inflammation	Itch	Inflammation	Directly Targets Bacteria	Safety Concerns	Continuous Use
Zabalafin hydrogel - Topical	✓	✓	✓	✓	✓	✓	✓
Crisaborole - Topical (PDE4)	✓	✓			✓	Sting	
Ruxolitinib - Topical (JAK Inhibitor)	✓	✓				FDA Box Warnings	
Roflumilast PDE4 (4 wks)	✓	✓				Drug Interactions Liver Effects	
Tapinarof Aryl Hydrocarbon Receptor Agonist (8 wks)	✓	✓				12.2% All TEAEs 8.1% Folliculitis	
Dupilumab - Injectable (IL-4Ra)	✓	✓				Pain Eye Problems	
Tralokinumab - Injectable (IL-13)	✓	✓				Pain Eye Problems	
Lebrikizumab - injectable (IgG4 monoclonal antibody (IL-13)	✓	✓				Higher incidence conjunctivitis vs placebo	
Nemolizumab-injectable (IL-31)	✓	✓				Headache	
Abrocitinib - Oral (JAK Inhibitor)	✓	✓				FDA Box Warnings	
Upadacitinib - Oral (JAK Inhibitor)	✓	✓				FDA Box Warnings	
Corticosteroids	✓	✓				Thinning Skin Others	
Calcineurin Inhibitors (Tacrolimus, Pimecrolimus)	✓	✓				FDA Box Warnings	

being effective for severe flares; however, these require cautious use due to the risk of atrophy and telangiectasia. TCIs offer steroid-sparing benefits, including tacrolimus and pimecrolimus. Emerging non-steroidal treatments, such as the topical PDE4 inhibitor crisaborole, JAK inhibitor ruxolitinib, and aryl hydrocarbon receptor (AhR) antagonist, tapinarof, relieve pruritus and prevent remission. Despite their widespread use and effectiveness, topical therapies alone often fail to control moderate to severe AD adequately or prevent flares, particularly when complicated by microbial colonization and systemic inflammation.[10-12]

Systemic therapies, including biologics (ie, dupilumab, tralokinumab, lebrikizumab, and nemolizumab), immunosuppressants (eg, cyclosporine, methotrexate, and azathioprine), and JAK inhibitors (ie, abrocitinib and upadacitinib), offer improved control for moderate to severe or refractory AD by targeting specific inflammatory pathways. For many, biologics remain the first-line systemic treatments for moderate to severe AD, although they are associated with substantial costs. JAK inhibitors are superior to biologics in the rapidity of reducing pruritus but require laboratory monitoring and have a boxed warning that includes major adverse cardiovascular events, among other warnings. Conventional immunosuppressants remain conditionally recommended but require continuous monitoring, while systemic corticosteroids are not recommended for ongoing AD treatment. Most systemic treatments are not recommended for patients aged 12 years or younger. Systemic treatments do not directly address critical factors such as *S. aureus* colonization, necessitating supplementary topical management and adjunctive antimicrobial interventions.[4,6,10-12]

Clinical practice guidelines emphasize the importance of a multifaceted approach to AD management that combines skincare, topical, systemic, and adjunctive therapies tailored to individual patient profiles.[10-12] Recent guidelines recommend incorporating daily barrier-restoring skincare products, particularly those containing ceramides, from an early age as preventive measures, alongside proactive topical anti-inflammatory treatments to manage mild-to-moderate cases.[5,11,12] For moderate to severe cases, guidelines advocate for the early initiation of systemic therapies and continuous adjunctive topical treatments to comprehensively address inflammatory and microbial aspects.[10-12] Ultimately, given the complexity of SAIGE factors influencing AD pathology, effective management necessitates a holistic and personalized therapeutic strategy that targets all aspects of the AD Continuum.[5,12] AD poses a significant unmet need for a single therapy effective against the entire Continuum of pathogenic *S. aureus* progression and infection. Despite advances in topical and systemic AD treatments, challenges persist in maintaining adequate disease control. AD treatment must be effective and safe long-term for both adult and pediatric patients, as AD prevalence is highest in early childhood. Effective AD management should restore eubiosis and skin barrier function, prevent the progression of pathogenic *S. aureus*, control inflammation and flares, and reduce pruritus and xerosis.[5,6] Increasing antimicrobial resistance must be considered when selecting AD treatment in this context.

Statement 5: *Zabalafin is a novel, botanically derived therapeutic that has shown benefits on multiple components of AD, including targeted S. aureus reduction.*

Zabalafin botanical hydrogel (formerly AB-101a) is a novel topical AD treatment that addresses the four devils of the AD Continuum: inflammation, dysbiosis, *S. aureus* colonization and infection, pruritus, and xerosis.[14] Zabalafin hydrogel is a single-source complex botanical considered a single agent by the FDA. It consists of multiple bioactive compounds with mechanisms of action that provide multi-targeted anti-inflammatory, antibacterial, antipruritic, and anti-xerosis activity. Furthermore, Zabalafin forms a barrier, or "liquid bandage," over the AD lesion, helping to restore microbiome balance and skin barrier function.[14]

Increasing antimicrobial resistance necessitates antibiotic stewardship when selecting AD treatment. Zabalafin has a broad antibacterial effect and is active against MRSA, with no antibiotic resistance reported. Furthermore, zabalafin displays antimicrobial activity via multiple mechanisms, reducing the risk of antibiotic resistance.[14]

A randomized, double-blind, vehicle-controlled phase 2a clinical trial evaluated the safety and efficacy of zabalafin hydrogel for treating AD in adults and children aged ≥2 years (n=41) over four weeks. The primary endpoint was the investigator global assessment (IGA) score, and secondary endpoints included the eczema area and severity index (EASI), pruritus, patient-oriented eczema measure (POEM), skin infection rating scale (SIRS), infection, and bacteriology. At trial enrollment, 81% of the cohort had mild AD, and 19% had moderate AD.[14] Zabalafin treatment significantly improved skin clearance, pruritus, inflammation, and quality of life, while effectively controlling AD flares by treating the skin bacterial microbiome. In a second, open-label phase 2a trial (n=19), zabalafin reduced AD inflammation in 50% of patients, as indicated by an IGA score of clear or almost clear at 12 weeks. Most patients experienced improvements in pruritus (68.4%) and quality of life (89%), as measured by POEM. Furthermore, in the pediatric cohort, a rapid pruritus reduction with an improvement of >4 on the Itch NRS was observed by day 4 and was sustained beyond the 4-week endpoint. A significant and steady improvement in the SIRS was observed with infections cleared in 84% of patients by day 15 and 100% of *S. aureus* isolates eradicated, including MRSA. This demonstrates normalization of the bacterial microbiome to minimize the likelihood of AD flares and *S. aureus* skin infection. Additionally,

zabalafin hydrogel was associated with minimal risk and high patient tolerability, with only one report of transient mild stinging, representing a corticosteroid-free option likely suitable for continuous, long-term AD treatment. Based on these data, zabalafin addresses the unmet need for a single topical agent for the treatment of mild-to-moderate AD, regardless of infection status, that is safe for long-term use.[14]

Statement 6: *Zabalafin addresses the Continuum of AD via:*

a) Mechanisms that disrupt bacteria and bacterial DNA
b) Mechanisms that inhibit the AD inflammatory cascade
c) Antipruritic mechanisms that attenuate afferent nerve signaling and release of substance P
d) Moisturizing properties that reduce xerosis
e) Lesion-healing properties that restore the skin barrier and resolve microbiome dysbiosis

Polyphenols within zabalafin hydrogel potentially act on various points in the inflammatory cascade. These polyphenols modulate immune cell regulation, proinflammatory cytokine synthesis, and gene expression.[19] They inhibit the AD inflammatory cascade through several mechanisms, including initiation and termination of the inflammatory cascade by inhibiting T-cell proliferation.[19] Through potent radical scavenging and metal ion chelation, polyphenols suppress NLRP3, inhibit reactive oxygen species (ROS) production, and promote ROS detoxification, thereby attenuating inflammation. Multiple polyphenol mechanisms disrupt or alter bacterial DNA and the cell membrane.[20] Evidence shows that polyphenols and the taspine alkaloid inhibit topoisomerase I and II, leading to bacterial DNA damage, and intercalate bacterial DNA, thereby disrupting transcription.[20,21] Polyphenols also change the permeability of the bacteria's cell membrane and block drug efflux transport, disrupting material entry and expulsion.[20] Polyphenols reduce pruritus through antipruritic mechanisms that attenuate sensory afferent nerve signaling and the release of the neuropeptide substance P.[22] Furthermore, polyphenols prevent substance P-induced inflammation by inhibiting the synthesis and release of substance P.[22]

The zabalafin hydrogel formula's lesion-healing properties restore the skin barrier, resolve microbiome dysbiosis, and reduce xerosis.[14] Forming an artificial skin barrier over the AD lesion can restore the activity of innate antimicrobial peptides and the host response inhibited by *S. aureus*. This facilitates the restoration of microbiome balance and skin barrier function. The moisturizing properties of the zabalafin hydrogel formula help reduce xerosis.[14] Thus, through its multiple mechanisms of action, zabalafin targets all components of the AD Continuum, including pathogenic *S. aureus* progression, infection, inflammation, pruritus, and xerosis.

Limitations

While this review highlights the evolving understanding of AD as a Continuum and introduces zabalafin as a promising multi-targeted therapy, several limitations must be acknowledged. The proposed AD Continuum paradigm emphasizes multifactorial SAIGE triggers, but variations in individual patient responses remain complex, reflecting the inherent heterogeneity of the disease. The SAIGE triggers involvement may differ by patient age, ethnicity, and geographical location, which were not explicitly dissected within this review. The clinical evidence supporting zabalafin is primarily derived from two phase 2a trials involving a relatively small number of patients (n=60) with mild-to-moderate AD, which may limit the generalizability of findings across diverse patient populations, age groups, severe or refractory disease cases, and long-term outcomes.

CONCLUSION

Atopic dermatitis is increasingly understood as a disease continuum characterized by interconnected and perpetuating inflammation, infection, pruritus, and xerosis. These manifestations are continuously influenced by the SAIGE factors, which collectively trigger, perpetuate, or exacerbate AD. *S. aureus* plays a unique role in the AD paradigm, linking colonization and microbiome dysbiosis directly to disease exacerbation and progression along the disease continuum. Given this complexity, conventional AD therapies that address isolated components of the disease often fail to provide comprehensive, sustained control across the AD Continuum. This underscores the unmet need for treatments that address the full spectrum of AD manifestations while minimizing adverse effects. Zabalafin botanical hydrogel represents an innovative therapeutic option with multi-targeted mechanisms that simultaneously address multiple facets of the AD Continuum: inflammation, microbiome dysbiosis, *S. aureus* colonization and infection, pruritus, and xerosis. Its various mechanisms of action, absence of reported antibiotic resistance, and potential suitability for long-term application address several unmet clinical needs. However, further research is warranted to validate its comparative effectiveness, long-term safety profile, and real-world applicability. Ultimately, therapies such as zabalafin, which comprehensively address the AD Continuum, hold significant promise for improving patient outcomes and simplifying the therapeutic approach to this complex and burdensome chronic disease. This paradigm shift underscores the importance of comprehensive approaches to AD management that address the full spectrum of manifestations in the AD Continuum.

DISCLOSURES

An educational grant from Alphyn Biologics, Inc., Cincinnati, OH, supported the research for this work. The authors (LAS, AAH, AA, PK, MEG, DPW, PL) received consultancy fees for attending a planning meeting in Orlando, FL, in March 2025, to create the research design for this work. All authors (LAS, AAH, AA, PK, MEG, DPW, PL) participated in designing the research for this work, finalizing the manuscript to report this research, and all agreed with the final content. All authors (LAS, AAH, AA, PK, MEG, DPW, PL) read and approved the final version of the manuscript and its publication.

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AUTHOR CORRESPONDENCE

Anneke Andriessen PhD

E-mail:..... ti016762@telfort.nl