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 ORIGINAL ARTICLE 

# Practical Algorithm on Topical Treatment of Flaring Atopic Dermatitis (AD) With or Without Secondary Infection

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## ABSTRACT

Acute exacerbations or flares are a key characteristic of atopic dermatitis (AD), often associated with sleep deprivation, as well as experiences of stigmatization, social withdrawal, anxiety, and depression. Local skin colonization with Staphylococcus aureus (SA) is a key contributor to AD, particularly to AD flares. Treating SA-driven active AD, especially in cases where skin that is secondarily infected complicates management, calls for a carefully balanced approach that serves to calm AD activity and clear local infection and SA related colonization. The methodological approach included a systematic literature review to inform an expert panel before a face-to-face meeting to develop a practice-based algorithm for managing AD flares with or without secondary infection. A panel of nine experts in dermatology, including both Board-certified dermatologists and pediatric dermatologists, engaged in a discussion followed by an online review to refine the algorithm and to provide clear guidance on the topical treatment of flaring AD with or without AD skin that is secondarily infected. The algorithmic recommendations emphasize a need for therapy that addresses both skin inflammation and local SA colonization and/or infection, underscoring the unmet need for multi-targeted topical therapies such as zabalafin hydrogel, a novel approach under current investigation for persons with active AD, including flaring and secondary infected AD. This novel practice-based algorithm aims to improve outcomes for all AD patients, especially those with frequent flares or secondary infections and highlights the importance of balancing efficacy with antibiotic stewardship.

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## INTRODUCTION

Atopic dermatitis (AD), a chronic, relapsing inflammatory skin condition that affects approximately 20% of children and up to 10% of adults, is characterized by xerosis, localized or diffuse erythematous scaly patches, and usually intense pruritus.[1] AD is associated with sleep disruption for patients of all ages, decreased work productivity, depression, and anxiety, which all carry additional health and economic burdens for patients and those in their households.[1,2] There is also a well-established association between AD and other morbidities. As such, AD development in an individual often marks the beginning of the "atopic march," a term used to describe the increased risk of developing one or more of the other diseases as part of atopy, including asthma, food allergy, and allergic rhinitis.[3,4]

AD is viewed as predisposing an individual to acute exacerbations and recurrent bacterial and viral skin infections.[4] Unlike healthy individuals and those with certain other inflammatory skin conditions such as psoriasis, up to 90% of patients with AD are colonized with *Staphylococcus aureus* (SA).[5] SA plays a significant role in AD, producing enterotoxins that disrupt the skin barrier, enhance type 2 inflammation, and contribute to AD exacerbations and infectious complications.[5]

A critical factor for SA skin colonization in AD patients is an imbalance in the local skin microbiome. Patients with AD typically have (in both lesional and non-lesional skin) a reduced diversity of beneficial, commensal bacteria, which protects the skin by regulating the immune reactivity and outcompeting pathogens such as SA.[5] In AD, the deficiency in these protective bacteria allows SA to colonize, potentially exacerbating AD. Both decreased skin microbiome diversity and increased SA abundance have been observed during AD flares.[6,7] Reducing SA colonization, restoring microbiome diversity, and normalizing skin barrier function serves to resolve AD flares and AD chronicity.[7]

Current approaches to managing AD typically target the immuno-inflammatory cascade, leaving xerosis, pruritus, and the exacerbating factor of SA for eventual resolution. It remains problematic that typical regimens for AD management do not adequately treat AD skin that is secondarily infected by bacteria. Although topical and/or systemic antibiotics are often prescribed for AD skin that is secondarily infected, with systemic antibiotics typically when the infection is more widespread,[8] more than half of adults with moderate to severe AD report inadequate disease control.[9,10] No single product is broadly effective against all typical manifestations of active AD: pruritus, inflammation, damaged skin barrier, and local SA skin infection.[8]

Designed to address this long-overdue practice gap, a recent advance in AD management illustrates the particular value of developing a practice-based treatment algorithm. Our armamentarium now approaches the inclusion of a novel agent, zabalafin hydrogel (AB-101a, Alphyn Biologics, Annapolis, MD) – a multi-targeted topical drug with mechanisms of action that provides antipruritic, anti-inflammatory, and broad antibacterial, including anti-MRSA, activity.[11] Zabalafin is designed to address the unmet need for a mono-therapeutic approach to the safe and effective topical management of active AD, including flares, by reducing pruritus, inflammation, and localized bacterial skin colonization and/or local clinical skin infection, and importantly for patients of all ages, with no restrictions on long-term continuous use in chronic active AD.[11]

## MATERIALS AND METHODS

This project aimed to develop a practical algorithm for the topical treatment of AD and SA-driven exacerbations of AD. Algorithm development began by defining the project and selecting an expert panel. Then, a systematic review of the literature on the topical management of flares in mild-to-moderate AD, with or without secondary infection, was performed.

### Role of the Panel

The expert panel (n=9) of pediatric dermatologists, dermatologists, and scientists who are focused on treating patients with AD convened on March 10, 2024, in San Diego, CA, to provide insights into the topical treatment of mild-to-moderate AD and *S. aureus*-driven AD exacerbation, including new advances in therapy designed to improve patient care and outcomes. During the face-to-face meeting, the results of the systematic review were discussed by the panel, and a practice-based algorithm was drafted based on published evidence and the panel's experiences and opinions. After the face-to-face expert panel meeting, the authors used an online process to fine-tune the algorithm, after which the manuscript was drafted for review and publication.

### Literature Search

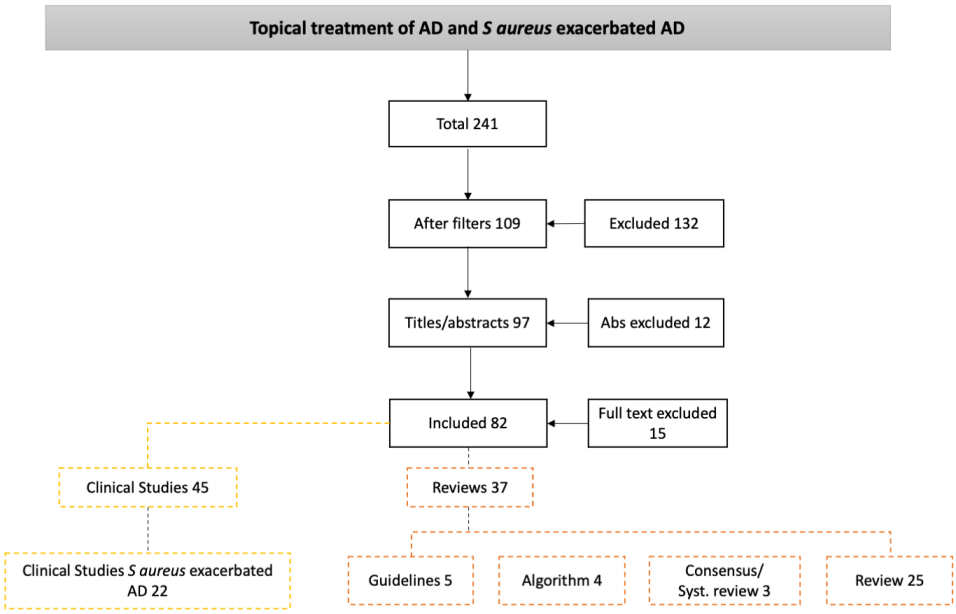
A systematic review of English-language literature on the topical treatment of mild-to-moderate AD and *S. aureus*-infected AD was conducted on January 17 and 18, 2024, using PubMed, with Google Scholar as a secondary source. The search criteria used are outlined in Table 1. Searches included clinical trials, research studies, clinical guidelines, consensus papers, and reviews (providing original data), published between January 2010 and January 2024. Selected articles were based on their clinical relevance to AD and topical treatments for *S. aureus*-infected/secondary-infected AD. Excluded publications were non-English and articles that did not include patients with mild-to-moderate AD and *S. aureus*-infected AD addressed with topical treatment. The searches yielded 82 articles that qualified for inclusion (Figure 1) and were deemed clinically relevant to inform current best practices in topical AD treatment with or without AD skin that is secondarily infected (n=45 clinical studies and n=37 reviews, such as treatment guidelines, algorithms, consensus reports, systematic reviews, among others).

**TABLE 1.**

| Search Terms | |
|---|---|
| Pediatric Atopic Dermatitis and *Staphylococcus aureus* Infection Topical Treatment Atopic Dermatitis/ Impetiginized Atopic Dermatitis | Pediatric/childhood AD* |
| | AND epidermal barrier dysfunction OR Sa infection OR impetiginized OR skin dysbiosis OR Sa-related AD exacerbation OR localized infection OR MRSA |
| | AND clinical AD topical treatment guidelines OR algorithms OR consensus papers OR topical treatment OR TCS OR TCI OR PDE-4 I OR Zabalafin OR topical antimicrobial OR antimicrobial resistance OR topical antibiotic OR topical antibiotic resistance OR bleach baths |

Atopic dermatitis (AD); *Staphylococcus aureus* (Sa); methicillin-resistant *Staphylococcus aureus* (MRSA); Topical corticosteroids (TCS); Topical calcineurin inhibitors (TCI)

**FIGURE 1.** Results of systematic literature searches.




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

**TABLE 2.**

| Guidelines, Algorithms, and Systematic Reviews | | |
|---|---|---|
| **Treatment Guideline/Algorithm/Consensus Paper** | **Includes Topicals for AD** | **Reference** |
| Guidelines (Section 2) for topical therapies for AD (2014) | Yes | Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;71(1):116–132 |
| Guidelines of care for the management of atopic dermatitis in adults with topical therapies | No | Sidbury R, et al. *J Am Acad Dermatol.* 2023; doi: org/10.1016/j.jaad.2022.12.029 |
| Strategies for using corticosteroids in children and adults with eczema | Yes | Lax SJ, et al. Cochrane Database of Systematic Reviews. 2022(3) |
| Consensus recommendations and AD algorithm | Yes | Lynde CW, et al. *J Cutan Surg.* 2019;23(3_suppl):35-13S |
| Consensus-based European guidelines for the treatment of AD, 2018, Part I and Part II | Yes | Wollenberg A, et al. Part I. *J Eur Acad Dermatol Venereol* 2018;32:657–682. Part II *J Eur Acad Dermatol Venereol.* 2018; 32:820-878 |
| Development of a clinical pathway for atopic dermatitis patients: a case-based approach | Yes | Guenther LC, et al. *J Am Acad Dermatol.*2016;15(12):1485-1494 |
| Do Antimicrobial Resistance Patterns Matter? An Algorithm for the Treatment of Patients With Impetigo. | Yes | Schachner LA, et al. *J Am Acad Dermatol.* 2021;20(2):134-142 |
| Treatment of Impetigo in the Pediatric Population: Consensus and Future Directions | Yes | Schachner LA, et al. *J Am Acad Dermatol.* 2020;19(3):281-290 |
| Algorithm for the management of atopic dermatitis in people with skin of color | Yes | Alexis AF, et al. *J Am Acad Dermatol.* 2023;22(8)(Suppl 2)s3-10 |
| Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review | Yes | Bath-Hextall FJ, et al. *Br J Dermatol.* 2010;163(1):12-26 |
| Bleach baths for atopic dermatitis: A systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE | Yes | Bakaa L, et al. *Ann Allergy Asthma Immunol.* 2022;128(6):660-668 e9 |
| Current guidelines and recommendations for the management of skin and soft tissue infections | No | Montravers P, et al. *Curr Opin Infect Dis.* 2016;29(2):131-8 |

Atopic dermatitis (AD)
Few guidelines address racial/ethnic-specific skincare as an individual approach to AD

Publications of reviews that included AD treatment guidelines, algorithms, and consensus papers (n=12) selected for inclusion were from various regions (Table 2). Although some of these reviews include a section devoted to topical treatment for AD, few of these selected reviews address racial/ethnic-specific skincare in the context of active AD.

## RESULTS

### A Practice-Based Algorithm for Atopic Dermatitis

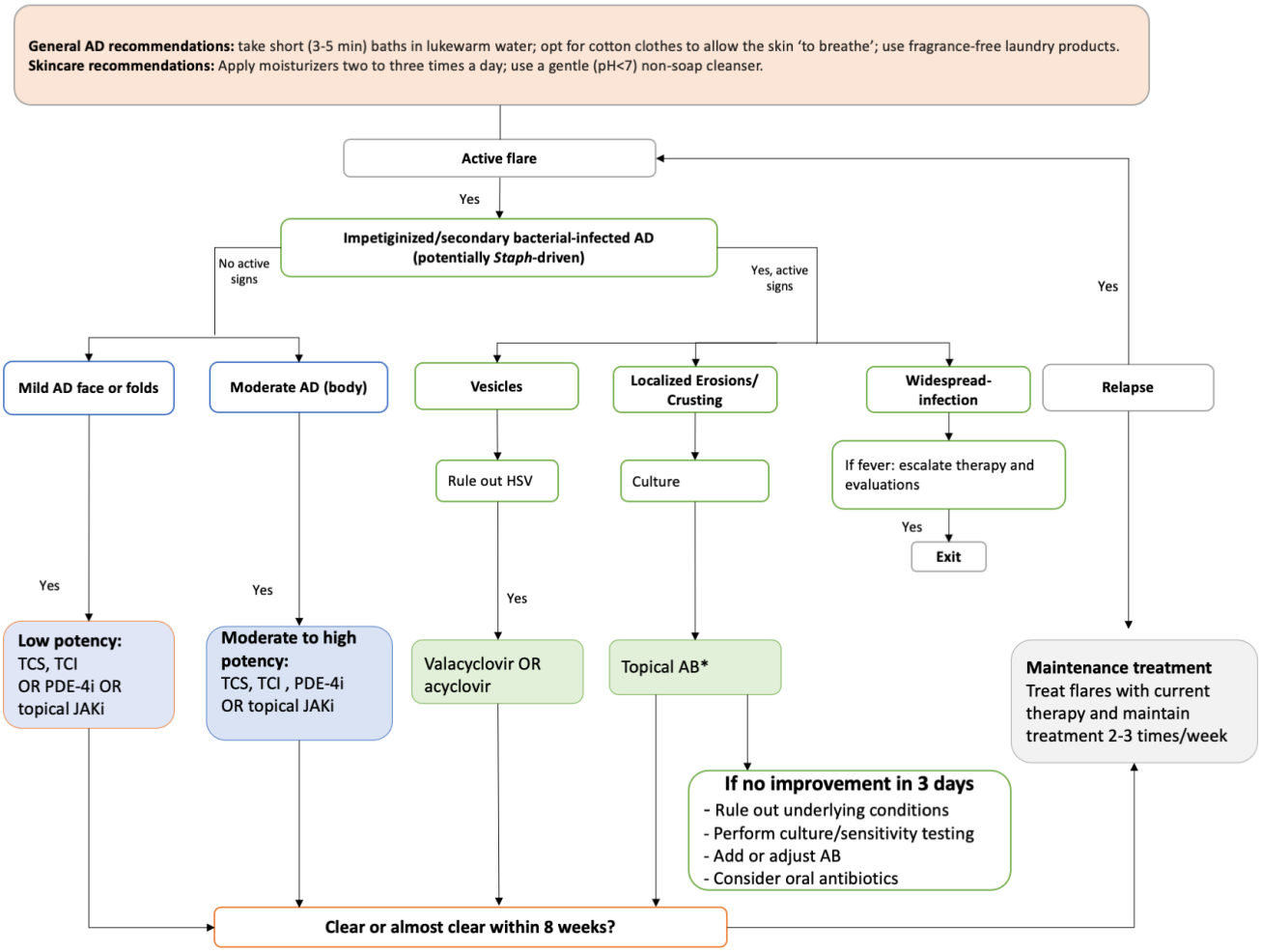
After advisors workshopped a draft algorithm prior to the expert panel meeting, the panel deliberated and agreed to a version based on the literature review results and their expert experiences and opinions (Figure 2). The algorithm is conveyed in two sections: treating active AD flares with non-infected skin and treating secondarily infected AD flares.

*Active Atopic Dermatitis Flare*

Acute exacerbations or flares are part of the relapsing and remitting nature of AD. Flares are generally defined as worsening disease requiring escalation and/or treatment intensification.[12,13] When evaluating AD severity, clinicians should consider factors such as xerosis, erythema, oozing, swelling, excoriations, lichenification, and the extent of clinically evident affected areas. Several assessment tools are available to gauge AD severity, including the Investigator Global Assessment (IGA), the Eczema Area and Severity Index (EASI), and the Scoring Atopic Dermatitis (SCORAD) scales.[14]

AD flares can significantly affect patients' physical and psychosocial well-being and are associated with high levels of sleep deprivation, stigmatization, social withdrawal, anxiety, and

**FIGURE 2.** Practical algorithm on topical treatment of flaring AD with or without secondary infection.




Topical *antibiotic (AB) eg: Ozenoxacin, mupirocin or retapamulin

**TABLE 3.**

**Common Topical Corticosteroids for the Treatment of Atopic Dermatitis**

| Potency | Class | Corticosteroid | Preparation |
|---|---|---|---|
| Ultra-high | I | Clobetasol propionate 0.05% | Ointment, cream, foam |
| High | II | Mometasone furoate 0.1% | Ointment |
| Medium to high | III | Betamethasone valerate 0.1% | Ointment, cream, lotion, foam |
| Medium | IV | Triamcinolone acetonide 0.1% | Ointment, cream |
| Medium to low | V | Hydrocortisone valerate 0.2% | Ointment, cream |
| Low | VI | Desonide 0.05% | Ointment, cream, foam, gel |
| Very low | VII | Hydrocortisone 0.25 – 1% | Ointment, cream, lotion, solution |

Note: These are common topical corticosteroids from each potency class; however, this is not an exhaustive list.[19]

depression.[15] After an AD flare, hyperpigmentation (dyschromia) may persist for weeks to months, especially in patients with dark skin phototypes.[16] As a result, patients with AD, especially skin of color patients with AD, may present with pigmentary sequelae (hyper-hypo- and even depigmentation) that may impact their quality of life. Early treatment to mitigate the risk of AD-associated inflammation and pigmentary sequelae may improve outcomes.[17]

Treatment approaches for AD flares vary based on the severity and location of symptoms.

*Topical Treatment of Non-Infected Atopic Dermatitis*

Emollients remain the cornerstone of treatment for AD, regardless of level of AD severity, with the intent to reduce xerosis, decrease transepidermal water loss, improve skin barrier function, and reduce pruritus.[2,4] Emollients typically need to be applied 2 to 3 times a day, preferably to include application immediately after bathing.[2] A Cochrane review that assessed moisturizers containing humectants, lipids, and/or ceramides reported that daily use reduced the rate of flares and enhanced the efficacy of topical corticosteroid treatment.[2,15]

When routine moisturizing does not control AD symptoms, anti-inflammatory topical therapy is typically added and continued until adequate control is achieved.[15] Topical anti-inflammatory therapies include corticosteroids, calcineurin inhibitors, phosphodiesterase 4 (PDE-4) inhibitors, and selective Janus kinase (JAK) inhibitors.[18]

*Topical corticosteroids*

Topical corticosteroids (TCSs) are a first-line anti-inflammatory treatment (Table 3). In the United States, they can be classified by locally vasoconstrictive potency from weakest (class VII) to most potent (class I).[18]

TCSs can be applied to acutely erythematous skin to address an active AD flare and the associated pruritus.[18] Low-potency TCS products are considered appropriate for face and body folds and the very young, while high-potency TCSs are typically utilized for young adults or older, particularly for chronic and lichenified lesions. For long-term management of AD, the least-potent corticosteroid that is effective should be used to mitigate the risk of adverse effects.[19] However, during acute AD flares, the use of mid- or higher-potency TCSs for short courses may be appropriate to gain rapid control of symptoms.

Potential side effects of TCSs include skin atrophy, purpura, telangiectasia, striae, impaired wound healing, allergic contact dermatitis, and acneiform or rosacea-like eruptions on the face. The potential for these and other side effects should be discussed with the patient to improve adherence and to minimize the likelihood of under- as well as over-treatment.[15]

*Topical Calcineurin Inhibitors (TCIs)*

Both tacrolimus ointment and pimecrolimus cream are currently approved for AD treatment. Pimecrolimus, 1% cream, is indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate AD for ages 2 and above. Meanwhile, tacrolimus ointment is indicated as second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe AD, with tacrolimus 0.03% ointment approved for ages 2 and above, and tacrolimus 0.1% ointment approved in patients aged 16 years and above.[20,21] Although there are no head-to-head trials, tacrolimus 0.1% ointment is considered more effective than pimecrolimus 1% cream for pruritus in AD patients, with a vasoconstricting potency similar to that of a mid-potent topical corticosteroid.[18]

Topical Calcineurin Inhibitors (TCIs) can be used on all areas of the body and face, as they have not been found to induce skin atrophy. As a result, they may be preferred over TCS in sensitive areas such as the eyelid region, the perioral skin, the genital area, the axilla region, or the inguinal fold.[15,18]

Potential side effects of TCIs include short-term skin burning, warmth sensation, and pruritus, especially when applied to acutely erythematous skin. Patients should be made aware of these potential side effects to minimize the likelihood of premature discontinuation of treatment.[15] Patients should

minimize UV exposure by using sunscreen and appropriate clothing and avoid combining TCI with phototherapy.[18]

Initial concerns about an increased risk of lymphoma from animal studies led the US Food and Drug Administration (FDA) to issue a boxed warning for TCIs. However, subsequent observational studies in humans did not find convincing evidence of an elevated risk for lymphoma with chronic TCI use. Nevertheless, clinicians should be aware of the boxed warning and discuss the essential elements of the warning with patients to optimize compliance and address patient concerns.[18]

*PDE-4 Inhibitors*

The topical PDE-4 inhibitor crisaborole is approved for the treatment of mild-to-moderate AD in patients 3 months of age and older in the United States.[22] In 2 multicenter, randomized, double-blind trials, crisaborole 2% ointment demonstrated a higher success rate in improving AD compared to the vehicle. At day 29, 32.8% and 31.4% of subjects treated with twice daily crisaborole 2% ointment achieved treatment success (defined as clear or almost clear skin with a 2-grade improvement) compared to 25.4% and 18.0% in the vehicle groups for Trials 1 and 2, respectively. The most common adverse reaction was application site pain.[22] However, an examination of local tolerability data from the crisaborole Phase 3 clinical trial shows a burning/stinging rate of over 49% for the active and over 56% for the vehicle.[23]

Roflumilast 0.15% cream is approved in the United States for topical treatment of mild to moderate AD in patients 6 and older.[24] This medication should be applied to affected areas once daily. In two multicenter, randomized, double-blind, vehicle-controlled trials, 0.15% of roflumilast cream demonstrated a higher success rate in improving mild to moderate AD compared to vehicle. At week 4, 32.0% and 28.9% of subjects treated with roflumilast achieved treatment success (defined as clear or almost clear skin with a 2-grade improvement per vIGA) compared to 15.2% and 12.0% in the vehicle groups for Trials 1 and 2, respectively.[23] The most common adverse reactions reported in the clinical trials were headache, nausea, application site pain, diarrhea, and vomiting.[24]

*Topical JAK Inhibitors*

Ruxolitinib 1.5% cream is the first topical JAK inhibitor approved by the FDA for the short-term and non-continuous treatment of mild to moderate AD in non-immunocompromised patients 12 years of age and older, with application to affected areas of up to 20% BSA. Applied to affected areas twice daily, ruxolitinib works by blocking JAK1 and JAK2, which are involved in cytokine pathways that contribute to skin inflammation. In clinical trials, more than 50% of patients had clear or almost clear skin and/or significantly less itch after applying ruxolitinib cream twice a day for 8 weeks.[25] The most common adverse reactions with ruxolitinib cream for AD were nasopharyngitis, diarrhea, bronchitis, ear infection, increased eosinophil count, urticaria, folliculitis, tonsillitis, and rhinorrhea. However, ruxolitinib cream also carries a boxed warning for the risk of serious infections, a higher rate of major adverse cardiovascular events, thrombosis, lymphoma, and other cancers, and a higher rate of all-cause mortality.[25]

*Zabalafin Hydrogel*

Current therapeutic approaches for the management of AD typically focus on the inflammatory and pruritic components of the disease and/or have side effects and safety warnings that restrict continuous use over a chronic period of time. Zabalafin hydrogel, a novel advance in the treatment of AD, is completing phase 2b studies, and is designed to broadly address not only the inflammation and pruritus but also to address the bacterial component of AD, leading to a restoration of microbiome diversity and skin barrier function.[26] Zabalafin has demonstrated significant improvements in itch, quality of life, and inflammation (50 % of patients experienced a reduction of the inflammation component of AD as indicated by >2 improvements in the IGA score and IGA score achieving clear or almost clear at 12 weeks), clearance of infection on AD skin, and control of SA-associated AD flares in both children and adults.[11,26] Zabalafin is associated with minimal risk and high patient tolerability, representing a corticosteroid-free option that may be appropriate for continuous, long-term use in a chronic disorder such as AD.[26]

A randomized, double-blind, vehicle-controlled four-week trial evaluated the safety and efficacy of zabalafin hydrogel for treating AD in individuals ages 2 and older, including both children and adults (n=41). In the trial, 81% of subjects had mild AD and 19% had moderate AD at enrollment. Data from the first cohort of the Phase 2a clinical trial showed significant skin clearance, itch reduction, and control of AD flares by treating the bacterial microbiome on the AD skin. A significant and steady improvement in the Skin Infection Rating Scale (SIRS) was seen throughout the 4-week trial, demonstrating normalization of the bacterial microbiome in the active AD skin environment to aid in the management of AD flares and minimize the likelihood of SA skin infection. Furthermore, in the pediatric group, a rapid itch reduction with an improvement of >4 on the Itch NRS was demonstrated by ay 4 and was sustained even after the dosing stopped.[27]

*Topical Treatment of Mild AD on the Face and Body Folds*

Mild AD affecting the face and/or body folds can be treated with low-potency TCSs, TCIs, PDE-4 inhibitors, or a topical JAK inhibitor. When treating the face (especially the peri-orbital region) and/or other sensitive areas such as body folds and the neck, topical corticosteroids should be limited to low potencies due to the increased risk for local adverse reactions and systemic absorption. Regularly monitoring the amount of TCS applied

**TABLE 4.**

**Antiviral Drugs for the Acute Treatment of Eczema Herpeticum Owing to Herpes Simplex Virus[5]**

| Drug | Suggested Adult/ Adolescent Dose | Suggested Pediatric Dose | Comments |
|---|---|---|---|
| Acyclovir | Oral: 200-400 mg/ dose 5 times daily | ≥2 y: Oral 20 mg/kg/dose 4 times daily (max 800 mg/dose) | Typical duration 7-14 d<br>Parenteral (IV) administration is available in more severe cases<br>Needs to be adjusted for abnormal renal function |
| Valacyclovir | Oral (typical): 1 g twice daily<br>Oral (alternative): 500 mg 3 times daily | ≥3 mo: Oral: 20 mg/kg/dose twice daily (max 1000 mg/dose) | Off-label<br>Typical duration is 5-7 days<br>Limited pediatric data |

over time is also important to ensure efficacy and safety.[18,19] Furthermore, TCIs may be more appropriate for sensitive areas such as the face and folds, as these topicals do not have the risk of skin atrophy but may be limited by tolerability issues.[18]

*Topical Treatment of Moderate AD on the Body*

Moderate AD can be treated with moderate- to high-potency TCSs, TCIs, or PDE-4 inhibitors. Once- to twice-daily use of a potent TCS for 3 to 6 days is usually sufficient for treating diffusely distributed flares, followed by a quick taper in corticosteroid potency.[15]

*Active Atopic Dermatitis Flares With Signs of Secondary Infection, Potentially Driven by Staph aureus:*

Patients with active AD have an increased risk of developing a secondary bacterial infection, which causes significant morbidity.[6] In some cases, these infectious complications necessitate short hospitalizations to regain disease control. However, hospitalization for AD has been associated with an 8.3-year reduction in lifespan, underscoring the need for effective management to prevent severe outcomes.[28] *S. aureus* is most often responsible for secondary infection of AD. Areas of the skin that have become secondarily infected with bacteria like *S. aureus* can be referred to as "impetiginized lesions".[29] These localized SA infections may be associated with increased pruritus and more intense erythema, as well as local pigment changes manifested as hyper- or hypopigmentation and even local depigmentation may occur. When untreated and there is a progression of the local SA infection associated with active AD, the lesions may be characterized by the appearance of weeping, honey-colored crusts, and occasionally pustules and vesicles.[6,29] If a secondary infection of AD skin is suspected, the treatment depends on the clinical presentation and, if not predominantly SA-associated, then treatment varies depending on the pathogen.[15]

*Vesicles*

Impetiginous lesions in patients with AD can present with fluid-filled blisters (bullous impetigo), which may be confused with eczema herpeticum (EH).[5] EH is usually caused by infection with herpes simplex virus (HSV)-1 and manifests as pruritus and/or pain and the presence of vesicles, punched-out erosions, and/or hemorrhagic crusts.[5] This viral infection manifests most frequently on the face, neck, upper trunk, and antecubital/popliteal areas with active AD and is often accompanied by fever, malaise, and lymphadenopathy.[6] If patients present with vesicles, it is important that HSV be ruled out and appropriate treatment with valacyclovir or acyclovir be initiated (Table 4).

For mild cases of EH, oral acyclovir or oral valacyclovir can be considered. Valacyclovir has 3 to 5 times higher bioavailability than oral acyclovir, allowing for less frequent dosing while achieving plasma concentrations similar to those of parenteral acyclovir.[5] For patients with extensive skin involvement with EH, signs of systemic illness, and those less than 1 year of age, parenteral acyclovir should be considered.[5] Topical antivirals do not provide an appreciable benefit in HSV mucocutaneous disease and do not have a role in the treatment of EH.[5]

*Localized Erosions/Crusting*

Secondary infection of AD skin may warrant short-term topical and/or systemic antibiotic treatment. Topical antibiotics are recommended for patients with limited SA skin infection, whereas oral antibiotics are used for patients with severe secondary-infected AD.[30,31] When selecting an appropriate antibiotic, antimicrobial resistance must also be considered.[8] Increasing resistance or tolerance to antimicrobials that may be used in the treatment of SA skin infections in those with active AD is now well-documented and includes drugs such as fusidic acid, mupirocin, clindamycin, retapamulin, chlorhexidine, neomycin, and bacitracin.[32–35] Practicing responsible topical antibiotic stewardship is essential to preserve the efficacy of emerging topical antimicrobials. Antibiotics should also be used only for short periods and not long-term to minimize the likelihood of antibiotic resistance.[15]

When patients present with lesions suspicious of skin infection associated with active AD, including erosions and crusting,

**TABLE 5.**

**Topical Antibiotics for Impetiginized Lesions[36]**

| Order | Name of Drug | Dosing Regimen | Age Indication | Antimicrobial activity |
|---|---|---|---|---|
| 1 | Ozenoxacin 1% cream | BID/ 5 days | 2 months of age and older | Gram-positive bacteria, especially *S. aureus* including MRSA or *S. pyogenes*. Efficacy against mupirocin-resistant *S. aureus*, fusidic acid resistant *S. aureus*, quinolone-resistant *S. aureus*, and clindamycin-resistant *S. aureus*. |
| 2 | Mupirocin 2% ointment, 1% ointment for children aged 2 months to 16 years | TID/ 7-10 days | 2 months of age and older | Gram-positive bacteria, especially *S. aureus* including MRSA and *Streptococci*. |
| 3 | Retapamulin 1% ointment | BID/ 5 days | 9 months of age and older | *S. aureus* (methicillin susceptible isolates only and *S. pyogenes*. |
| 4 | Fusidic acid | TID/ 7-10 days | No age limitation stated in the PI | *S. aureus, Streptococcus spp. And Corynebacterium minutissimum.* |

Twice daily (BID), Three times daily (TID), *Staphylococcus aureus (Staph aureus), Methicillin resistant Staphylococcus aureus (MRSA)*

cultures may be performed to confirm infection and to identify the pathogen.[15] In localized cases, defined as fewer than ten lesions and smaller than a 36 $cm^2$ affected area, and in those that are systemically stable and those with a low risk for complications, topical ozenoxacin 1% cream, mupirocin 2% ointment, retapamulin 1% ointment, or fusidic acid 2% cream are recommended (Table 5).[36] Patients should be instructed to cleanse the skin and gently remove the crusts before applying a topical antibiotic.[36] Patients with acute, erosive, and oozing lesions may first be treated with wet wraps with diluted or lower potency corticosteroids until the oozing stops.[18]

Zabalafin hydrogel has been shown to be effective in treating the SA-associated complications of AD. A Phase 2a trial evaluating zabalafin hydrogel in patients (n=19) with infected AD skin met all endpoints for safety and efficacy. All patients showed a steady decrease in SIRS score, demonstrating good control of SA and MRSA, associated with AD flares. Seventy four percent of patients with AD achieved a SIRS score improvement of >6 points and 84% of patients with infected AD skin were cleared at the end of treatment. Compared to baseline, the trial also demonstrated significant and clinically relevant improvements in pruritus, patient-assessed quality-of-life indicators, and inflammation (50% of patients experienced a reduction of the inflammation component of AD as indicated by IGA score improvement >2 and IGA score achieving clear or almost clear at 12 weeks). There was one reported treatment-emergent adverse event of mild transient stinging in 1 or 2 study visits for 3 participants, indicating that the study had minimal side effect issues and favorable patient tolerability.[26] The Phase 2a results indicate that topical zabalafin may be viewed as a therapy that can not only treat active AD without associated SA skin infection but also may prove to be useful for active AD flares associated with local SA skin infection. This broad coverage for active AD with or without local SA skin infection could serve to improve patient adherence and may serve to minimize the need for polypharmacy in the management of AD. Moreover, since zabalafin works through multiple mechanisms of action for active AD, with or without SA infection, zabalafin may therefore prove to be associated with reduced concerns for the development of drug resistance.[26]

Dilute bleach baths have been proposed to suppress epidermal SA load and ultimately reduce AD severity without increasing the risks for antibiotic resistance. As such, these are recommended in multiple clinical practice guidelines. However, a recent meta-analysis showed that water baths were as effective as bleach baths at 4 weeks in pooled analyses; importantly, there were no significant quantitative differences for SA in patients treated with bleach vs water baths.[37]

If the skin does not improve following treatment, clinicians should rule out other underlying conditions and do culture and sensitivity testing. For patients treated with oral antibiotics, the choice of antibiotic should be adjusted based on the culture and sensitivity test results. If a severe active AD flare worsens or fails to improve within three days, hospitalization should be a consideration.[36]

*Widespread Infection*

A seven-day course of oral antibiotics is recommended in the case of widespread infection. Oral antibiotics are also appropriate if the patient has a fever or extensive lymphadenopathy, in which case hospitalization is indicated. In cases with no MRSA involvement, dicloxacillin, cephalexin, erythromycin, or amoxicillin-clavulanate can be prescribed. For MRSA-suspected or confirmed cases, clindamycin, trimethoprim/ sulfamethoxazole (TMP-SMX), tetracycline, telavancin, or daptomycin are recommended.[36]

*Maintenance Treatment*

Once the AD flare clears, maintenance treatment is recommended. Patients can stay on their maintenance therapy, administered daily or reduced as applicable to two to three times per week. Maintenance therapy may reduce the likelihood of flares and should be considered in patients with frequently relapsing active AD.[15] TCSs may be used proactively 1 to 2 times per week, or TCIs or PDE-4 inhibitors may be used 2 to 3 times per week after AD stabilization to minimize the likelihood of recurrent flares.[15] Due to the favorable efficacy, safety, and tolerability profile, zabalafin could be a desirable candidate for chronic maintenance of AD.

## LIMITATIONS

AD is a complex condition influenced by numerous genetic, immunological, microbiota, and environmental factors. This manuscript primarily focuses on managing AD flares with or without AD skin that is secondarily infected; a detailed discussion of the genetic, immunological, and environmental factors that contribute to AD flares is outside the scope of this paper. Although the role of SA in AD is well-documented, data on the contribution of microbial diversity to disease pathogenesis and treatment outcomes are limited. While the inclusion of pigmentary sequelae (hyper- hypo- and depigmentation) as a concern in AD acknowledges racial/ethnic differences, the existing literature does not adequately address how treatment regimens may need to be adapted for diverse skin phototypes. Lastly, the systematic literature search did not look at moderate to severe AD and was also limited to English-language literature, which may have excluded relevant studies published in other languages, particularly those focusing on regional variations in SA prevalence and management strategies in the context of active AD.

## CONCLUSION

All clinicians involved in managing AD play an essential role in treating AD flares to minimize the burden on patients and improve their quality of life. Despite advances in topical and systemic treatment options for AD, challenges persist in effectively and safely managing AD. The upcoming significant advance in AD therapeutics with the advent of topical zabalafin points to the need for an evidence-based/practice-based algorithm to assist in updating and guiding AD management. With its anti-pruritic, anti-inflammatory, and antibacterial properties, zabalafin hydrogel may address an unmet need for a single comprehensive topical therapy that has shown promising results in modulating the SA component of AD, controlling SA-related flares and infections, and is associated with minimal side effects, thus representing a steroid-free option with a positive safety and tolerability profile that may make zabalafin appropriate for continuous, long-term use. Moreover, further research is always warranted to advance clinical practice and particularly to promote antibiotic stewardship and to disseminate knowledge about emerging treatment options that are vital steps in addressing this challenge.

## DISCLOSURES

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Dr Lio reports being on the speaker's bureau for AbbVie, Arcutis, Eli Lilly, Galderma, Hyphens Pharma, Incyte, La Roche-Posay/L'Oreal, Pfizer, Pierre-Fabre Dermatologie, Regeneron/Sanofi Genzyme, Verrica; reports consulting/advisory boards for Alphyn Biologics (stock options), AbbVie, Almirall, Amyris, Arcutis, ASLAN, Astria Therapeutics, Bristol-Myers Squibb, Burt's Bees, Castle Biosciences, Codex Labs (stock options), Concerto Biosci (stock options), Dermavant, Eli Lilly, Galderma, Janssen, LEO Pharma, Lipidor, L'Oreal, Merck, Micreos, MyOR Diagnostics, Pelthos Therapeutics, Regeneron/Sanofi Genzyme, Sibel Health, Skinfix, Suneco Technologies (stock options), Soteri Skin (stock options), Theraplex, UCB, Unilever, Verdant Scientific (stock options), Verrica, Yobee Care (stock options). In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a Board member and Scientific Advisory Committee Member emeritus of the National Eczema Association.

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