

Consensus Recommendations on Adjunctive Topical Management of Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD) is well-recognized as a very common chronic and relapsing pruritic skin disorder affecting both children and adults worldwide. The adverse effects on the quality of life of affected individuals and their families is well-established. The pathophysiology of AD is complex, leading to interindividual variations in clinical presentation and severity. The chronicity of AD, characterized by periods of exacerbation and remission, supports a strong need to develop measures that can effectively and safely prolong remissions between flares of the disease. This article provides an overview of AD including prevalence, severity, and disease course/progression, succinct summaries of pathophysiology and medical management, and discussion of epidermal barrier dysfunction and skin microbiome shifting associated with AD. Additional emphasis is placed on adjunctive topical skin barrier approaches that may prolong disease-free remissions. Results from a panel of dermatologists queried about adjunctive approaches to AD, using a modified-Delphi approach, are also discussed.

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GENERAL OVERVIEW OF ATOPIC DERMATITIS

Atopic dermatitis (AD) is a commonly encountered heterogenous eczematous disorder that typically starts in infancy and early childhood, and may persist into adulthood; chronic-recurrent nature, associated pruritus, and genetic predisposition are all hallmarks of AD.[1,2]

Whether or not AD is a single disease entity or a spectrum of diseases with a shared phenotype is not completely understood, however, certain clinical features are highly characteristic. These include usual morphology and anatomic distribution of dermatitis, marked pruritus, relapsing course or seasonal variation, associated xerosis, and a personal or family history of atopy.[1-4] With regard to diagnostic criteria for AD, the Hanifin and Rajka criteria have long been the standard used in most textbooks and clinical studies, however, several other criteria have been developed, especially in Europe and Asia.[3,4] The emergence of newer diagnostic criteria reflect the desire to encompass variations in AD phenotype among different ethnic populations.[4] What appears to be shared among various diagnostic criteria is the presence of a chronically relapsing and highly pruritic eczematous dermatitis that usually starts within the first 2 to 5 years of life, exhibiting a tendency for anatomic sites of predilection especially during the childhood and adolescent years. A positive parental history of AD is a very important factor, as the risk for development of AD is doubled if present in one parent and tripled if both parents are affected.[2] Interestingly, the prevalence of AD is higher in urban areas and in more affluent and well-developed countries.[2]

Prevalence

Depending on study methodology, the prevalence of childhood AD is estimated to range from 6% to 12.98%, with data from a United States (US) population-based survey reporting a steady increase from 8% in 1997 to >12% in 2010 and 2011.[5] Data from 2012 showed a peak in AD prevalence in early childhood (14%) that persisted throughout childhood (13-14%), followed by a decrease during adolescence (8%) that remained stable throughout adulthood (6-8%).[5]

Severity

The severity of AD encompasses three major areas: (1) symptomatology, which includes pruritus and interference with sleep; (2) skin lesion findings such as erythema, scaling, crusting, lichenification, and excoriations; and (3) the body surface area affected.[5]

Importantly, these characteristics require both subjective reporting and professional objective evaluation. A large population-based study of AD from the United Kingdom (UK) that incorporated dermatologist evaluation showed severity rates of 84% with mild disease, 14% with moderate disease, and 2% with severe disease.[6] Despite variability among different states, population-based US survey data on severity of childhood AD from 2007-2008 noted mild disease in 67%, moderate disease in 26%, and severe disease in 7%, encompassing an estimate of 2.98 million children with moderate-severe AD.[5,7] Notably, severity of AD tends to be greater in the African-American/black population.[5]

Course of Disease

A systematic review and meta-analysis inclusive of 45 studies from 15 countries (N=110,651; 434,992 patient-years) evaluated persistence of AD.[8] From the time of diagnosis, 80% of childhood AD did not persist by 8 years and <5% persisted by 20 years. Children with onset of AD by age 2 years were less likely to exhibit persistent disease. This large-scale analysis showed that most childhood AD remitted by adulthood, although children with already persistent disease, later onset of AD, and/or AD of marked severity are more likely to experience greater AD persistence.[8] The early onset of AD, severe early AD, family history of atopy, female gender, black race, low income, and presence of filaggrin gene mutations have all been correlated with higher disease activity and greater likelihood of a more prolonged course.[9] Persistence of AD into adulthood often reflects cases of greater severity, with added clinical presentations such as hand eczema and/or lichenified nummular dermatitis.[10]

Progression of Disease

The recurrent nature of AD places patients on an unfortunate 'roller coaster pattern' characterized by periods of flare and remission; unfortunately, there is a relative lack of data on definitive patterns and time-courses of AD recurrence.[9] However, what is evident is that intermittent flares do occur, and that fluctuations in AD intensity and clinical presentations emerge over time.[9] In a given individual with AD, their inherent pathophysiologic makeup, the timing and nature of environmental conditions and exposures, and both when and how they have specifically utilized skin care products and medical therapies all can impact directly on the frequency, intensity, and duration of their AD flares over time. Regardless of whether AD is primarily a disease of the epidermal barrier (outside in theory), or is a primary systemic process with epidermal barrier dysfunction occurring as a secondary phenomenon (inside out theory), there are several inherent abnormalities present within normal-appearing skin of people with AD that characterize their chronic predisposition to develop both xerosis and eczematous flares.[9,11-19] These abnormalities, referred to collectively as atopic skin, include differences in stratum corneum (SC) lipid composition and content, reduction in epidermal antimicrobial peptides, changes in SC enzyme function, decreased epidermal humectancy (filaggrin gene mutations), altered cutaneous microflora with increased staphylococcal colonization, changes in the dendritic cell population, and increased presence of cutaneous T lymphocytes (T cells).[2,9,11-25] This supports the concept of subclinical inflammation in AD that is present between flares, with transition to an active flare occurring when atopic skin is triggered by a variety of potential exacerbating factors (ie, allergens, irritants, bacterial toxins, psychosocial stimuli, climatic changes). Atopic skin is not able to elicit effective repair mechanisms to correct epidermal barrier impairments that lead to flares of AD.[11-14,17,18] Therefore, in order to reduce the frequency of AD flares, it is important to incorporate long term management approaches that serve to maintain physiologic SC function in atopic skin and support the diversity and relative stability of the cutaneous microbiome that is present in normal-appearing skin.[9,12,25-30] Interestingly, there are data to support that early intervention of topical skin barrier therapy during the neonatal period may delay or prevent the emergence of clinical signs of AD.[9]

Newer Data on Disease Course/Progression

More recently, there are data to suggest that maintaining diversity of the cutaneous microbiome is important in the acute and long term management of AD.[23,26,29,30] For some time, it has been well-recognized that flares of AD correlate with an increased density of *S. aureus* at eczematous skin sites.[23] However, it is now apparent that flares of AD are also associated with a decrease in the diversity of skin bacteria and other microbial organisms, reflecting the importance of trying to sustain stability and diversity as a component of managing AD.[29,30] Data supporting this concept is reviewed in more detail below.

Pathophysiologic Mechanisms

Although a complete discussion of AD pathophysiology is beyond the scope of this article, a review of contributory pathogenic mechanisms serves to better understand both the acute and long-term management of AD. Several components contribute to the complex pathophysiology of AD including genetic and environmental factors, epidermal barrier dysfunction, dysregulation of innate and adaptive immune responses, decreased antimicrobial peptides (AMPs), aberrant activation and homing of T lymphocytes, role of specific dendritic cells, effects of certain cytokines and chemokines, overexpression of phosphodiesterase-4 (PDE4), augmented itch-scratch cycle, neuroimmunologic factors, and shifting of the cutaneous

microbiome during both flares and remission.[2,23,24,31-35] Table 1 depicts pathophysiologic mechanisms associated with AD.

The complexity of AD pathophysiology underscores the need for a well-designed management plan. Optimal treatment of AD incorporates thorough patient/family education, identification and avoidance of potential triggers, proper integration of topical skin barrier products, and rational selection and use of specific medical therapies. The objectives of AD management are two-fold: (1) marked reduction of the symptoms and signs of the acute flare and (2) long term control of AD with prolonged maintenance of remission. Ultimately, individualized selection of therapies for AD warrants consideration of both objectives.

Pharmacologic Management

Pharmacologic management of AD includes both topical and systemic agents, with selection based primarily on the severity of AD, patient age, and response to previous therapies. The following summarizes agents that are commonly used to treat AD.

Topical Agents

Topical corticosteroids (TCs)

TCs have been the mainstay of anti-inflammatory therapy for AD for >6 decades.[27] They are primarily used to rapidly control AD flares. Prolonged TC application is limited by local adverse events (AEs), with systemic AEs a concern with widespread and prolonged use.[26,27,36,37] Once the AD flare is stabilized, application of low-mid potency TCs twice weekly to sites of predilection (proactive therapy) can effectively reduce the frequency of subsequent flares.[26,27] Adjunctive use of a well-formulated moisturizer is important with TC therapy, as even short term use of TCs applied to human skin has been shown to delay SC barrier recovery, with murine studies noting impairment of both lamellar body production and epidermal lipid synthesis.[12,38]

Topical calcineurin inhibitors (TCIs)

Pimecrolimus cream (1%) and tacrolimus ointment (0.03%, 0.1%) are TCIs approved in the US as second-line agents for short-term and non-continuous treatment of AD in patients ≥2 years of age.[27,39,40] TCIs are not associated with the AEs seen with prolonged use of TCs.[26,27] Judicious use of TCIs for AD as initial monotherapy or in combination approaches can reduce the need for TCs, and have also shown success in repigmentation of hypopigmented macules and patches.[27] Proactive use of topical tacrolimus has been effective and safe in both children and adults with AD.[26,27] Although multiple studies support the overall safety of TCIs, "black box" warnings regarding potential malignancy risks appear in the approved product labeling with both TCIs based on theoretical concerns from animal studies.[26,27,39,40]

Topical phosphodiesterase-4 inhibitors (PDE4I)

Crisaborole 2% oinment is the only available topical PDE4I, approved in the US for AD in patients ≥2 years of age.[41] The approved labeling allows for application to any affected cutaneous sites, and does not restrict duration of use. Efficacy for signs and symptoms of AD and favorable safety were established in clinical trials, with the only relevant AEs being local tolerability reactions in 2-4% of subjects.[41-44] As with TCIs, topical crisaborole is not associated with the AEs seen with prolonged TC use, and available data support the absence of systemic safety signals or drug accumulation.[41-45]

Topical antimicrobials

Use of topical and/or systemic antibiotic therapy is recommended for treatment of cutaneous bacterial infections in AD, but not for chronic administration to suppress staphylococcal colonization and/or flares of AD.[46] However, data are lacking on the use of non-antibiotic antimicrobial/antiseptic therapies in the long-term management of AD. [26,27] Well-designed controlled studies are needed to evaluate clinical improvement and flare reduction with these agents.

Systemic Agents

Refractory and/or severe cases of AD sometimes require use of systemic therapy. Short course corticosteroid therapy may be used very selectively for rapid control, although prolonged use is best avoided due to AEs.[2,26] Dupilumab is a fully human anti-IL-4 receptor-alpha monoclonal antibody that inhibits IL-4 and IL-13 signaling, approved in the US for adults with inadequately controlled moderate to severe AD; the recommended dose is 300 mg injected subcutaneously every 2 weeks.[47] Efficacy and overall favorable safety have been confirmed in both short term and long term studies, both as monotherapy and in combination with TC therapy.[47-49] Conjunctivitis may be seen in some patients, and is usually manageable without discontinuation of therapy.[47-50] Oral immunosuppressive agents, such as cyclosporin and azathioprine, are used as second and third line agents, respectively, in refractory/severe cases of AD.[2,26] Careful monitoring is warranted with oral immunosuppressive therapy, with data on long term use relatively limited in AD, especially with azathioprine.[26] Importantly, topical barrier repair therapies (ie, moisturizers) are recommended adjunctively in patients using systemic therapy for AD.[12,26,27]

Adjunctive Topical Barrier Repair Approaches and Impact on Pathophysiology

The skin of AD patients is known to exhibit innate structural and functional abnormalities of epidermal/SC barrier functions.[11-13,17,18] These include increased TEWL that is worsened during AD flares, abnormal SC lipid composition, inability to sustain SC hydration, augmented immunologic/inflammatory responses to exogenous stimuli, and decrease in AMP levels and activity.[11-22] The latter factor, combined with microfissuring associated with xerotic skin, leads to an altered cutaneous microbiome in non-lesional, xerotic, and eczematous atopic skin.[12,20-23,51]

TABLE 1.

Pathophysiologic Mechanisms Associated With Atopic Dermatitis

Factor	Comments
Genetic	Several susceptible gene loci identified; genome wide and single nucleotide polymorphisms noted. Gene variations in epidermal barrier function, keratinocyte differentiation, innate and adaptive immune response, cytokines/chemokines. Loss-of-function FLG gene mutations. Mutations in AMPs and PRR with increased susceptibility to infection. Reduced claudin1 gene expression causing decreased epidermal tight junctions. Tmem79/matt gene polymorphism affecting lamellar granular proteins involved in lipid processing.
Environmental	Increased AD prevalence in urban setting. Lower AD prevalence with less indoor heating and higher relative humidity. >85% IgE-sensitized to house dust mite (HDM). Polyvalent IgE sensitization with inhalant and/or food allergens (extrinsic). Increased susceptibility to allergic and/or irritant contactants.
Epidermal/Stratum Corneum Barrier Dysfunctions	Lesional skin with 3-fold to 5-fold increase in TEWL compared to non-lesional skin in AD; TEWL increased 2-fold in normal or xerotic skin (non-eczematous skin) during AD flares; decreased SC hydration causes diminished enzymatic function and impairment of physiologic desquamation. Impaired intercellular lamellar membrane due to decreased ceramide content and ceramide: cholesterol ratio leading to increased TEWL. FLG gene mutations in 15% to 50% of AD patients causing decreased SC humectancy (reduced NMFs). Reduction in tight junctions adversely affecting lipid and FLG processing via altered skin pH. Increased skin pH in AD promotes bacterial colonization and enhanced serine protease activity, the latter causing structural protein and lipid degradation, leading to increased TEWL and decreased SC hydration/impaired water gradient.
Innate Immunity Dysregulation	Reduction in AMPs (cathelicidin [LL-37], human-beta-defensins 2 and 3) causing increased bacterial colonization and susceptibility to infections. Decreased expression of TLR2 causing altered SC tight junction integrity and lowered defense against *S aureus* and HSV infections.
Adaptive Immunity Dysregulation	Th2 proliferation by allergen/pathogen-activated DCs; Th2 cell cytokines impair SC lipid production and expression of SC proteins in acute lesions, activate mast cells and eosinophils to release factors that induce pruritus; IL-31 elicits pruritus. Activated keratinocytes elicit TSLP expression amplifying Th2 inflammation via activation/ migration of dermal DCs and priming of Tcells to produce IL-4, IL-5, and IL-13. Th2 driven increases in IL-4 and IL-13 elicit SC barrier dysfunction (decreased ceramides, decreased FLG, decreased involucrin and loricin, reduced AMPs) and promotes potential allergic inflammatory cascades (increased IgE, enhanced eosinophil migration, increased Th2 differentiation, augmented IL-31 expression). Th2 inflammation downregulate SC structural proteins comprising the keratinocyte cornified envelope (loricin, involucrin) and FLG. Th22 upregulation in acute AD and enhanced in chronic AD; IL-22 associated with epidermal hyperplasia and inhibited differentiation.
Dendritic Cell Augmented Activity	Various DC types contribute to AD lesions, including myeloid and plasmacytoid DCs. IDECs contribute to T cell activation. dDCs contribute to acute AD lesion formation and express high concentrations of TSLP.
Phosphodiesterase-4 Overexpression	PDE4 is the predominant intracellular cAMP degrading enzyme in keratinocytes, eosinophils, neutrophils, macrophages, T cells, monocytes, and fibroblasts. Overexpression of PDE4 implicated in AD; Augmented Th2 signaling; PDE4 inhibition suppresses Th2 and Th1 cytokines.
Itch-Scratch Cycle Augmentation	Release of TSLP, IL-13, and IL-31 upregulates pruritogens and stimulates neural fibers.
Neuroimmunologic Factors	Increased plasma levels of NGF and SP correlate positively with AD activity; BDGF prolongs eosinophil survival and augments chemotaxis.
Cutaneous Microbiome Shifting (Altered Commensal Competition)	*S aureus* colonization in >90% of AD patients. Toxin-producing *S aureus* associated with elicitation and/or prolongation of AD flares. Worsening of AD associated with altered skin microbiome (decreased bacterial diversity) especially at anatomic sites of predilection. Flared AD skin shows lower bacterial diversity with dominance of staphylococci (ie, *S aureus*). Effective AD therapy and non-flared AD skin show greater bacterial diversity with increases in specific genera (*Corynebacterium, Propionibacterium, Streptococcus*). Shift to lower bacterial diversity combined with staphylococcal dominance a marker for AD flaring.

FLG – filaggrin; AMPs – antimicrobial peptides; PRR – pattern recognition receptors; AD – atopic dermatitis; TEWL – transepidermal water less; SC – stratum corneum; NMFs – natural moisturizing factors; TLR –Toll-like receptor; *S aureus* – *Staphylococcus aureus*; HSV – *Herpes simplex virus*; DCs – dendritic cells; IL – interleukin; TSLP – thymic stromal lymphopoietin; IDECs – inflammatory dendritic epidermal cells; dDCs – dermal dendritic cells; PDE4 – phosphodiesterase-4; NGF – nerve growth factor; SP – substance P; BDGF – brain derived growth factor; References: 2,3,11-23,30-35,51

The increased colonization of atopic skin with *S aureus* is well-established.[2,11,12,20-23,51] However, what has been recognized more recently as a component of AD pathophysiology is a pattern of dysbiosis, characterized by a temporal association between AD flares and cutaneous microbiome shifting that decreases overall bacterial diversity and further increases staphylococcal predominance relative to other skin bacteria.[29,30,52,53] This further decrease in commensal competition among bacteria inhabiting atopic skin is demonstrated by the increased qualitative and quantitative dominance of staphylococci during AD flares (ie, *S aureus*) relative to many other bacteria, especially at anatomic sites of predilection.[30,52-53] In a human genomic study, bacteria present on healthy skin (n=92) showed a microbial diversity with 250 different genera, as compared to non-lesional and lesional AD skin (n=49) showing a reduced microbial diversity of 154 genera and 137 genera, respectively.[54]

Interestingly, in a study of infants (N=149) with or without a family history of AD, at 3 months, *S aureus* was more prevalent on skin of infants who later developed AD.[55] When compared to age-matched unaffected infants, increased *S aureus* prevalence was noted at the time of AD onset and also at 2 months before AD onset, suggesting that earlier shifting in skin bacterial colonization may contribute to clinical onset of AD in infancy.

Why is *S aureus* colonization important in the pathophysiology of AD even when clinical infection is not present? The role of *S aureus* in AD pathophysiology appears to correlate with initiation of and/or prolongation of flares through several mechanisms, including release of superantigens (ie, enterotoxins); stimulation of Th2 activity through cellular production of thymic stromal lymphopoietin (TSLP) and other cytokines (ie, IL-1B, IL-6, TNFbeta); and release of an IgE-reactive protein (fibronectin-binding protein).[12,23,51]

Role of Adjunctive Moisturizer Use

The apparent question that emerges in management of AD is if adjunctive topical barrier repair approaches, primarily through use of moisturizers, can contribute therapeutic benefit through impact on the underlying pathophysiology of AD?

Pharmacologic agents may control flares of AD and sustain therapeutic benefit by modulating specific pathophysiologic pathways, but they may offer limited or adverse effects on the epidermal barrier.[2,26] Proactive use of some TCs and TCIs have been shown to prolong AD remission, however, these agents are applied only to sites of predilection and not diffusely to atopic skin which is known to be impaired even when AD is quiescent.[12,26,27]

Current recommendations for AD management based on both experience and some clinical trials recognize that moisturizer application increases skin hydration, decreases TEWL, reduces clinical signs (ie, erythema, scaling, fissuring) and pruritus of AD, can decrease topical prescription anti-inflammatory therapy required, and may lessen the frequency of AD flares.[12,26,27,56-59] Gentle, non-alkaline soap-free cleansers, preferably devoid of fragrances, along with rational bathing practices, are important when cleansing atopic skin.[12,27] There are a wide range of moisturizer and barrier repair formulations in the marketplace used to treat xerotic and atopic skin. Conventional moisturizers primarily contain occlusive agents and humectants which reduce TEWL and increase SC hydration.[12,60] Other formulations additionally incorporate ingredients designed to support SC functional and structural integrity, such as ceramides, pseudoceramides, niacinamide, shea butter, sphingosine, FLG degradation products, and specific oils.[12,57,60-62]

Current information on AD pathophysiology suggesting the altered cutaneous microbiome in atopic skin and the increase in staphylococcal predominance with reduction in overall microbial diversity noted with AD flares has led to further research in moisturizer development. There are data in patients with moderate AD (N=60) supporting that a fragrance-free moisturizer

TABLE 2.

Consensus Recommendation on Adjunctive Topical Barrier Repair

Discussion Item	Panel Comments / Evidence Support
Goals of Therapy	Reduction of signs and symptoms. Improve quality of life. Enhance epidermal barrier function. Reduce flares of atopic dermatitis. Improve education and compliance. Provide long term improvement of skin health.
Role of Moisturizer Use[a]	Integral to management of atopic dermatitis of all severities. Every day use recommended with frequency of application tailored by clinician. Contribute to decrease of signs and symptoms of disease. Prevent flares of atopic dermatitis. Reduce amount of topical ant-inflammatory therapy needed over time (decreased overall topical corticosteroid use).
Role of Cutaneous Microbiome[b]	Decreased microbial diversity can precede flares of atopic dermatitis. Augmenting microbial diversity of skin contributes to effective treatment of AD. Maintaining inherent cutaneous microbial diversity contributes to sustaining healthy and disease-free skin. Data on a designated prebiotic moisturizer with a specialized formulation technology has been shown to promote a more balanced and diverse skin microbiome.

[a]References: 11,12,26,27,30,56-62
[b]References: 23,29,30,51-55

formulation (product A) containing a medium of thermal water, proprietary to a spring in the town of La Roche Posay, France, a prebiotic biomass of non-pathogenic bacteria (*Vitreoscilla filliformis*), a selected carbon source (mannose), and ingredients supporting barrier repair (ie, shea butter, niacinamide, glycerin) applied over 28 days provided greater improvement in signs and symptoms of AD, lack of increase in staphylococci, and increased microbial diversity versus a comparator moisturizer (product B) containing ceramide, glycerin, and shea butter.[53] Importantly, these observed differences between formulations were more pronounced with relapse of AD. Other outcomes were a 2-fold higher relapse rate with product B versus product A (60% vs 30%) with use after completion of 15 days of drug treatment, with greater severity of flaring with product B.[53] It has also been noted that improvements in AD with treatment are preceded by increased cutaneous bacterial diversity.[52] These data suggest an additional adjunctive benefit related to skin microbiology that can positively impact on both short term and long term management, especially as AD is a chronic relapsing disorder.

This article now concludes with results from the panel of authors who met together on November 3, 2018 in Nashville, Tennessee. Two authors (LK, JH) presented data accumulated from a thorough literature review on the pathogenesis of AD, current management approaches, and adjunctive topical therapy of AD. Using a modified delphi approach, the panel were then queried on specific management considerations and provided their answers independently. The results were then culled together and collectively discussed, with the group outlining consensus recommendations for topical adjunctive AD management along with comments on evidence support (Table 2).

CONCLUSION

AD is a heterogenous inflammatory/eczematous disorder associated with genetic predisposition and a complex pathophysiology. This disorder usually starts in early life, is typified by chronicity with flares and remissions, and can persist into adulthood. Adjunctive topical barrier repair therapy can assist in the long-term management of AD by decreasing clinical manifestations and reducing flares. This occurs if well-designed formulations are used regularly to counter some of the recognized impairments in epidermal barrier function that are innate to atopic skin and further exacerbated during AD flares. Newer information on the role of cutaneous microbiome shifting associated with AD supports the development of adjunctive formulations that promote commensal competition by enhancing a balanced and diverse skin microbiome.

DISCLOSURES

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REFERENCES

1. Siverberg JI, Silverberg NB. Atopic dermatitis: a heterogenous disorder. *Dermatol Clin.* 2017;35:ix-x.
2. Bieber T, Prolss J. Atopic dermatitis. In: Gaspari A, Tyring SK, Eds. Clinical and Basic Immunodermatology, Springer-Verlag, London, 2008:193-206.
3. Wuthrich B, Schmid-Grendelmeier. Definition and diagnosis of intrinsic versus extrinsic atopic dermatitis. In: Bieber T, Leung DYM, Eds. Atopic Dermatitis, Marcel-Dekker, Inc. New York, 2002:1-20.
4. Bieber T. How to define atopic dermatitis? *Dermatol Clin.* 2017;275-281.
5. Silverberg JI. Public health burden and epidemiology of atopic dermatitis. *Dermatol Clinic.* 2017;283-289.
6. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol.* 1998;139:73-76.
7. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. *Pediatr Allergy Immunol.* 2013;24:476-486.
8. Kim JP, Chao LX, Simpson EL, et al. Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. *J Am Acad Dermatol.* 2016;75:681-687
9. Abuabara K, Margolis DJ, Langan SM. The long-term course of atopic dermatitis. *Dermatol Clin.* 2017;35:291-297.
10. Hanifin JM. Adult-onset atopic dermatitis: fact or fancy? *Dermatol Clinic.* 2017;299-302.
11. Del Rosso JQ, Levin J. Clinical relevance of maintaining the structural and functional integrity of the stratum corneum: why is it important to you? *J Drugs Dermatol.* 2011;10(10 Suppl):s5-12.
12. Del Rosso JQ, Levin J. The clinical relevance of maintaining the functional integrity of the stratum corneum in both healthy and disease-affected skin. *J Clin Aesthet Dermatol.* 2011;4:22-42.
13. van Smeden J, Bouwstra JA. Stratum corneum lipids: their role for the skin barrier function in healthy subjects and atopic dermatitis patients. *Curr Probl Dermatol.* 2016;49:8-26
14. Levin J, Friedlander SF, Del Rosso JQ. Atopic dermatitis and the stratum corneum: part 1: the role of filaggrin in the stratum corneum barrier and atopic skin. *J Clin Aesthet Dermatol.* 2013;6:16-22.
15. Levin J, Friedlander SF, Del Rosso JQ. Atopic dermatitis and the stratum corneum: part 2: other structural and functional characteristics of the stratum corneum barrier in atopic skin. *J Clin Aesthet Dermatol.* 2013;6:49-54.
16. Levin J, Fallon Friedlander S, Del Rosso JQ. Atopic dermatitis and the stratum corneum: part 3: the immune system in atopic dermatitis. *J Clin Aesthet Dermatol.* 2013;6:37-44.
17. Proksch E, Elias PM. Epidermal barrier in atopic dermatitis. In: Bieber T, Leung DYM, eds. Atopic Dermatitis. New York: Marcel Dekker; 2002:123–143.
18. DiNardo A, Wertz PW. Atopic dermatitis. In: Leyden JJ, Rawlings AV, eds. Skin Moisturization, 1st ed. New York: Marcel Dekker; 2002:165–178.
19. O'Regan GM, Irvine AD. The role of filaggrin in the atopic diathesis. *Clin Exp Allergy.* 2010:40:965–972.
20. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med.* 2002;347(15):1151–1160.
21. DiNardo A, Gallo RL. Cutaneous barriers in defense against microbial invasion. In: Elias PM, Feingold KR. Skin Barrier. New York: Taylor & Francis; 2006:363–377.
22. Howell MD, Wollenberg A, Gallo RL, et al. Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Immunol.* 2006;117:836–841
23. Leung DYM. Role of Staphylococcus aureus in atopic dermatitis. In: Bieber T, Leung DYM, Eds. Atopic Dermatitis, Marcel-Dekker, Inc. New York, 2002:401-418.
24. Orfali RL, da Silva Oliveira LM, de Lima JF, et al. Staphylococcus aureus enterotoxins modulate IL-22-secreting cells in adults with atopic dermatitis. *Sci Rep.* 2018;8:6665.
25. Czarnowicki T, Krueger JG1, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol.* 2017;139:1723-1734.
26. Prezzano JC, Beck LA. Long-term treatment of atopic dermatitis. *Dermatol Clin.* 2017; 35:335-349.
27. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71:116-132.
28. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol.* 2014;71:1218-1233.
29. Schommer NN, Gallo RL. Structure and function of the human skin microbi-

ome. *Trends Microbiol.* 2013;21:660-668.
30. Baldwin HE, Bhatia ND, Friedman A, et al. The role of cutaneous microbiota harmony in maintaining a functional skin barrier. *J Drugs Dermatol.* 2017;16:12-18.
31. Malik K, Heitmiller KD, Czarnowicki T. An update on the pathophysiology of atopic dermatitis. *Dermatol Clin.* 2017; 35:317-326.
32. Zebda R, Paller AS. Phosphodiesterase 4 inhibitors. *J Am Acad Dermatol.* 2018;78(3S1):S43-S52.
33. Bäumer W, Hoppmann J, Rundfeldt C, Kietzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. *Inflamm Allergy Drug Targets.* 2007;6:17-26.
34. Leyden JJ, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. *Br J Dermatol.* 1974;90:525-530.
35. Rudikoff D, Bos JD. Pathophysiology of atopic dermatitis and atopiform dermatitis. In: Rudikoff D, Cohen SR, Scheinfeld N, Eds. Atopic Dermatitis and Eczematous Disorders; CRC Press/Taylor & Francis Group, Boca Raton, 2014:107-144.
36. Warner MR, Camisa C. Topical corticosteroids. In: Wolverton SE, Ed. Comprehensive Dermatologic Drug Therapy, 3rd Edition, Elsevier-Saunders, Philadephia, 2013;487-504.
37. Del Rosso J, Friedlander SF. Corticosteroids: options in the era of steroid-sparing therapy. *J Am Acad Dermatol.* 2005;53:850–858.
38. Kao JS, Fluhr JW, Man MQ, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. *J Invest Dermatol.* 2003;120:456–464.
39. Prescribing information. Elidel (pimecrolimus) cream 1%. Valeant Pharmaceuticals North America LLC, Bridgewater, NJ. December 2017.
40. Prescribing information, Protopic tacrolimus ointment 0.03%, 0.1%. Astellas Pharma US Inc, Northbrook, IL. May 2012.
41. Prescribing information. Eucrisa (crisaborole) ointment 2%. Pfizer Laboratories (division of Pfizer Inc), New York, NY. November 2017.
42. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol.* 2016;75:494-503.
43. Hoy SM. Crisaborole ointment 2%: a review in mild to moderate atopic dermatitis. *Am J Clin Dermatol.* 2017;18:837-843.
44. Eichenfield LF, Call RS, Forsha DW, et al. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. *J Am Acad Dermatol.* 2017;77: 641-649.
45. Zane LT, Kircik L, Call R, et al. Crisaborole topical ointment, 2% in patients ages 2 to 17 years with atopic dermatitis: a phase 1b, open-label, maximal-use systemic exposure study. *Pediatr Dermatol.* 2016;33(4):380-387.
46. Del Rosso JQ, Rosen T, Thiboutot D, et al. Status report from the Scientific Panel on Antibiotic Use in Dermatology of the American Acne and Rosacea Society: part 3: current perspectives on skin and soft tissue Infections with emphasis on methicillin-resistant *Staphylococcus aureus*, commonly encountered scenarios when antibiotic use may not be needed, and concluding remarks on rational use of antibiotics in dermatology. *J Clin Aesthet Dermatol.* 2016;9:17-24.
47. Dupixent package insert
48. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* 2016;375:2335-2348.
49. Thomson J, Wernham AGH, Williams HC. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal. *Br J Dermatol.* 2018;178:897-902.
50. Wollenberg A, Ariens L, Thurau S, et al. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab-clinical characteristics and treatment. *J Allergy Clin Immunol Pract.* 2018 Feb 9. pii: S2213-2198.
51. Neiman AL, Lipoff J, Garner R, Lebow A, Cohen SR. The role of infectious agents in atopic dermatitis. In: Rudikoff D, Cohen SR, Scheinfeld N, Eds. Atopic Dermatitis and Eczematous Disorders; CRC Press/Taylor & Francis Group, Boca Raton, 2014:165-177.
52. Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res.* 2012;22:850-859.
53. Seité S, Zelenkova H, Martin R. Clinical efficacy of emollients in atopic dermatitis patients - relationship with the skin microbiota modification. *Clin Cosmet Investig Dermatol.* 2017;10: 25-33.
54. Seité S, Flores GE, Henley JB, et al. Microbiome of affected and unaffected skin of patients with atopic dermatitis before and after emollient treatment. *J Drugs Dermatol.* 2014;13:1365-1372.
55. Meylan P, Lang C, Mermoud S, et al. Skin colonization by *Staphylococcus aureus* precedes the clinical diagnosis of atopic dermatitis in infancy. *J Invest Dermatol.* 2017;137:2497-2504.
56. van Zuuren EJ, Fedorowicz Z, Christensen R, et al. Emollients and moisturizers for eczema. *Cochrane Database Syst Rev.* 2017 Feb 6;2:CD012119. doi: 10.1002/14651858.CD012119.pub2.
57. Chamlin SL, Kao J, Frieden IJ, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol.* 2002;47(2):198-208.
58. Msika P, De Belilovsky C, Piccardi N, et al. New emollient with topical corticosteroid-sparing effect in treatment of childhood atopic dermatitis: SCORAD and quality of life improvement. *Pediatr Dermatol.* 2008;25:606-612.
59. Grimalt R, Mengeaud V, Cambazard F, et al. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. *Dermatology.* 2007;214:61-67.
60. Del Rosso JQ. Moisturizers: function, formulation, and clinical applications. In: Draelos ZD, Ed. Cosmeceuticals, 2nd Ed, Saunders-Elsevier, Philadelphia, 2009;97-102.
61. Del Rosso JQ, Kircik LH. The integration of physiologically-targeted skin care in the management of atopic dermatitis: focus on the use of a cleanser and moisturizer system incorporating a ceramide precursor, filaggrin degradation products, and specific "skin-barrier-friendly" excipients. *J Drugs Dermatol.* 2013;12:s85-91.
62. Kircik L, Hougeir F, Bikowski J. Atopic dermatitis, and the role for a ceramide-dominant, physiologic lipid-based barrier repair emulsion. *J Drugs Dermatol.* 2013;12:1024-1027.

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