Ann Allergy Asthma Immunol 120 (2018) 10–22

Contents lists available at ScienceDirect

Special Article

Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape

Mark Boguniewicz, MD [*]; Luz Fonacier, MD [†]; Emma Guttman-Yassky, MD, PhD [‡]; Peck Y. Ong, MD [§]; Jonathan Silverberg, MD, PhD, MPH [‖]; Judith Rosen Farrar, PhD [¶]

[*] Division of Allergy–Immunology, Department of Pediatrics, National Jewish Health and University of Colorado School of Medicine, Denver, Colorado
[†] Section of Allergy and Immunology, NYU Winthrop Hospital, Mineola, New York
[‡] Department of Dermatology and the Immunology Institute, Icahn School of Medicine at the Mount Sinai Medical Center, New York, New York
[§] Division of Clinical Immunology and Allergy, Children's Hospital Los Angeles and Department of Pediatrics, University of Southern California, Keck School of Medicine, Los Angeles, California
[‖] Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois
[¶] Academic Services Connection, Inc, Canandaigua, New York

ARTICLE INFO

Article history:
Received for publication October 14, 2017.
Received in revised form October 25, 2017.
Accepted for publication October 31, 2017.

ABSTRACT

The implementation of treatment guidelines for atopic dermatitis is challenging, in part because of different guidance documents being used by different groups of specialists and in part because the language of guidelines often reflects the evidence base rather than the practical "how to." The Atopic Dermatitis Yardstick is part of a series developed in response to the need to proactively address the loss of disease control for atopic illnesses at all levels of severity. It presents a comprehensive update on how to conduct a sustained step-up in therapy for the patient with inadequately controlled or poorly controlled atopic dermatitis. Patient profiles, based on current guidelines and the authors' combined clinical experience, provide a practical and clinically meaningful guide to aid physicians in helping their patients achieve the goal of clear to almost clear. The intent is not to replace guidelines but to complement their recommendations incorporating the latest research and therapies.

© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease—one of the most common inflammatory skin diseases worldwide, with an estimated prevalence of up to 25% of children and 7% of adults in the United States.[1–5] AD typically occurs in infancy and early childhood, with an onset in the first year of life reported for 60% to 85% of children and by 5 years of age for at least 85%.[2,6–8] However, AD can present at any age; and although most childhood-onset symptoms resolve before adulthood, persistence (albeit some in milder forms) is relatively common.[1,9–13] Up to 50% of adult patients are first diagnosed in adulthood, and 30% of childhood cases persist into the adult years.[1,14–16] Managing AD at any age can be challenging.

Atopic dermatitis is a diagnosis based on clinical presentation.[9–11,17] Current research detailing the underlying mechanisms of AD (Fig 1; eCommentary 1)[18] holds hope that biomarkers will be available to confirm the diagnosis and possibly differentiate various AD phenotypes (eg, intrinsic vs extrinsic AD, pediatric AD, Asian-origin AD),[19–31] but the current reality is that AD is diagnosed by symptoms and exclusion (Table 1).[5,9,11]

The clinical presentation of AD is characterized by (1) pruritus, (2) eczematous lesions (associated with T-helper cell type [T_H] 2 and T_H22 inflammation), and (3) dry skin (related to epidermal barrier

Reprints: Mark Boguniewicz, MD, Division of Allergy–Immunology, Department of Pediatrics, National Jewish Health and University of Colorado School of Medicine, 1400 Jackson Street, Room J310, Denver, CO 80206; E-mail: boguniewiczm@njhealth.org.

Disclosures: Dr Boguniewicz is a member of the speakers' bureau and is a consultant for Regeneron and Sanofi-Genzyme and has done clinical research for Regeneron. Dr Farrar has no financial interests to disclose. Dr Fonacier serves on advisory boards for Regeneron and Genentech, is a member of the speakers' bureau for Regeneron, and has research receiving grant support from Baxter, Genentech, and Merck. Dr Guttman-Yassky serves on the boards of Sanofi-Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, Leo Pharma, AnaptysBio, Celsus, Dermira, Galderma, Novartis, Pfizer, Vitae, Glenmark, AbbVie, and Asana Biosciences; serves as a consultant for Regeneron, Sanofi Aventis, MedImmue, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, Drais, AbbVie, Anacor, AnaptysBio, Dermira, Galderma, Leo Pharma, Novartis, Pfizer, Vitae Mitsubishi Tanabe, Eli Lilly, Glenmark, and Asana Biosciences; and receives grant support from Regeneron, Celgene, BMS, Janssen, Dermira, Leo Pharma, Merck, Novartis, and UCB. Dr Ong has no financial interests to disclose. Dr Silverberg serves on advisory boards and as a consultant for AbbVie, Eli Lilly, Galderma, GlaxoSmithKline, Kiniksa, Leo, Menlo, Pfizer, Realm, Roivant, and Regenron-Sanofi; and has research receiving grant support from GlaxoSmithKline.

Funding Sources: American College of Allergy, Asthma and Immunology, including editorial support and an honorarium for each author.

https://doi.org/10.1016/j.anai.2017.10.039
1081-1206/© 2017 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

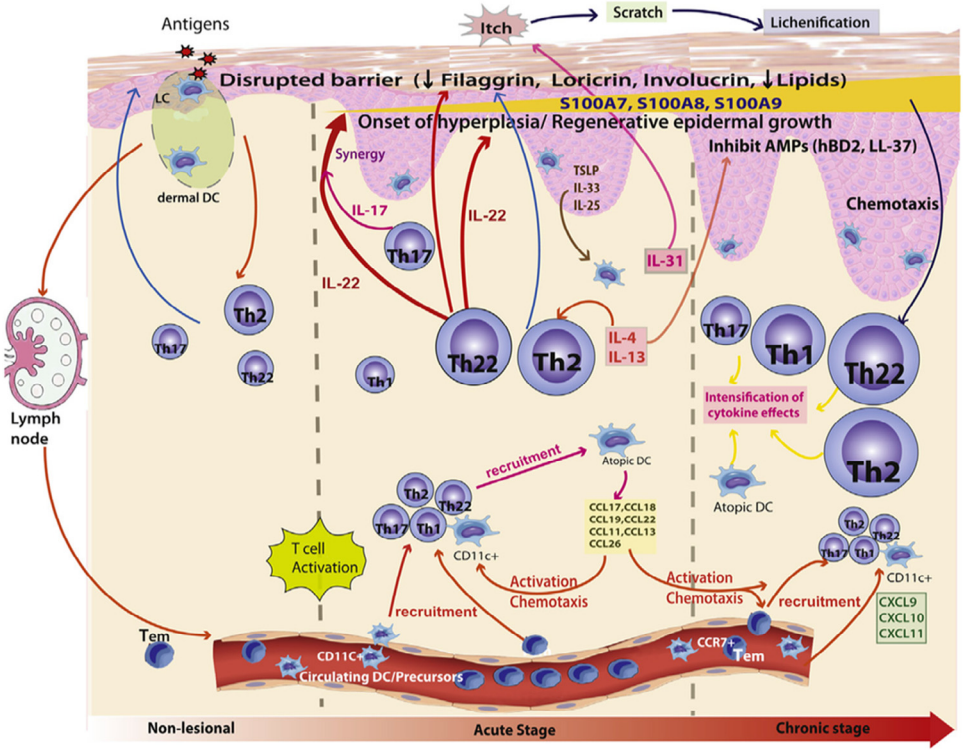

Figure 1. Immunopathologic mechanisms underlying atopic dermatitis. Reprinted with permission from Leung D, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol.* 2014;134:769–779,[18] with permission from Elsevier. AMP, adenosine monophosphate; CCR7, C-C chemokine receptor type 7; CXCL, chemokine ligand; DC, dendritic cell; hBD2, human β-defensin 2; IL, interleukin; Tem, effector memory T-cell; Th, T-helper cell type; TSLP, thymic stromal lymphopoietin.

dysfunction; Fig 1; eCommentary 1).[7,9–11,17,32] Pruritus is the hallmark of AD; and the cycle of itching and scratching exacerbates the cellular damage in skin lesions and facilitates secondary infections, which can be serious.[29,33–36] These patients are at increased risk for cutaneous infections, and in a recent study, also at risk for multiorgan and systemic infections.[37] Symptoms usually wax and wane, and patients with AD can present with a range of disease severity, from mild intermittent disease to severe difficult-to-control disease (Fig 2). For greater depth, the reader is directed to current guidelines and review publications.[7,9–11,17,32]

Current guidance documents recommend a "control-based" and "risk-based" model of disease management in which an initial diagnosis is followed by treatment according to categorization of severity[9–11] (Fig 2). However, for AD, validated measures to assess severity are not commonly used in the clinic, making it difficult to assess the impact of treatment and monitor disease progression. Although several validated clinical scoring systems are available, they are used mostly as tools for clinical research. Others await validation.[38–52] These are presented in Table 2. The Food and Drug Administration's (FDA) preferred primary efficacy end point categorizes AD severity according to a subjective, static Investigator's Global Assessment (IGA) or Investigator's Static Global Assessment (ISGA) score. The IGA has not been validated for AD in any setting.[1,48] The lack of validated clinical measures with standardized

Table 1
Diagnostic Criteria for Atopic Dermatitis[17]

Essential (must be present)	Important (supports diagnosis)	Associated (nonspecific but supports diagnosis)	Exclusionary (excludes diagnosis)
Pruritus	early age of onset	atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)	scabies
Eczema (acute, subacute, chronic)	atopy	keratosis pilaris, pityriasis alba, hyperlinear palms, ichthyosis	seborrheic dermatitis
Morphology—typical or atypical? Age-specific patterns:	personal and/or family history	ocular, periorbital changes	contact dermatitis (irritant or allergic)
Infants and children: facial, neck, extensor involvement	immunoglobulin E reactivity	other regional findings (eg, perioral changes, periauricular lesions)	ichthyoses
Any age group: current or previous flexural lesions; sparing of groin and axillary regions	xerosis	perifollicular accentuation, lichenification, prurigo lesions	cutaneous T-cell lymphoma
History—chronic or relapsing?			psoriasis photosensitivity dermatoses immune deficiency diseases erythroderma of other causes

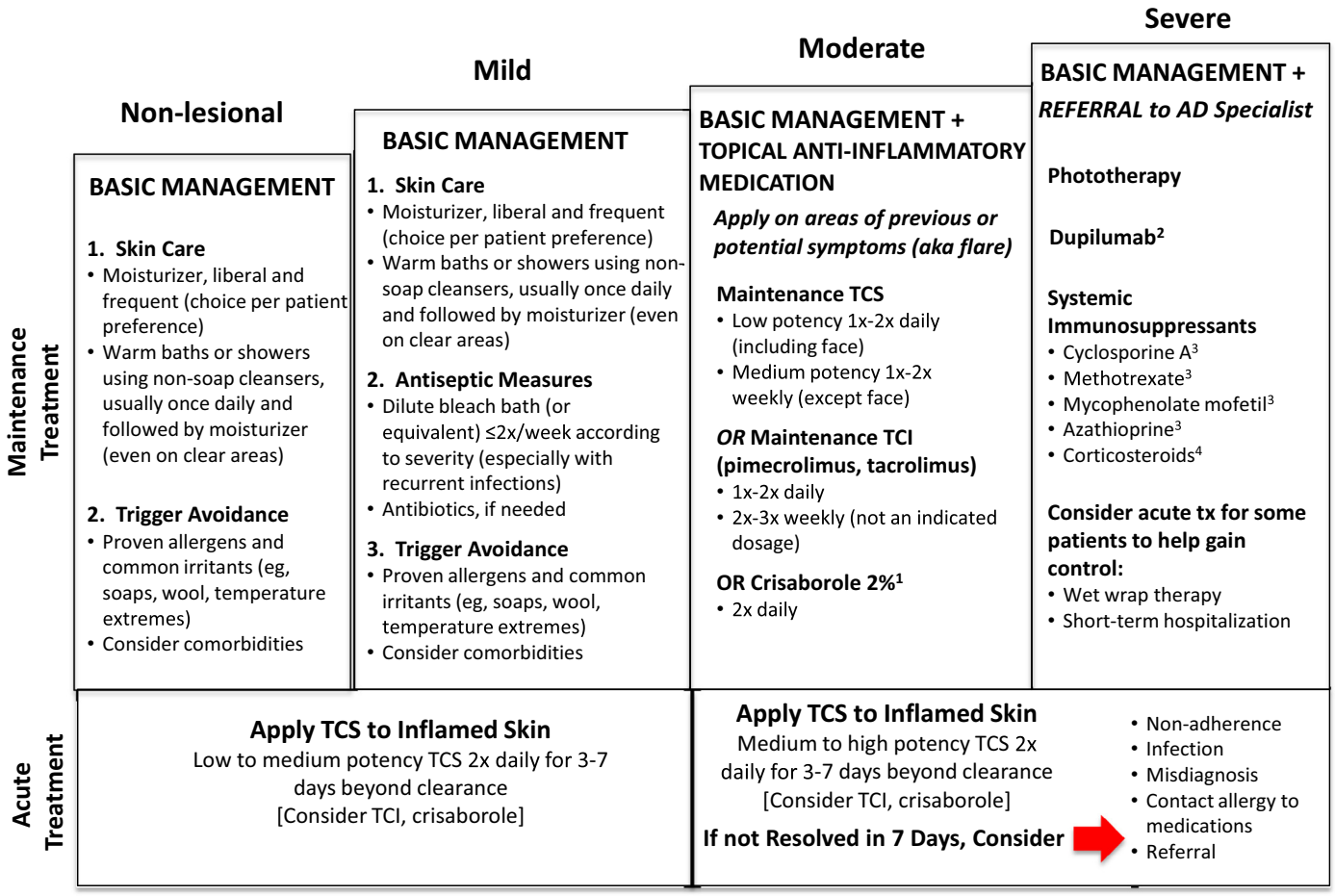

Figure 2. Step-care management of atopic dermatitis (AD).[17] [1]Indicated for patients at least 2 years old with mild to moderate AD.[74] [2]Indicated for patients at least 18 years old with moderate to severe AD.[80] [3]Not approved by the Food and Drug Administration to treat AD. [4]Approved by the Food and Drug Administration to treat AD but not recommended for long-term maintenance. A short course of systemic corticosteroids can help resolve severe symptoms, but exacerbation at discontinuation is common. Systemic corticosteroids also can be used as cotreatment during the initiation and optimization of phototherapy, other systemic immunosuppressants, or dupilumab. TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Tx, treatment.

definitions and implementation precludes any meaningful comparisons, which in turn impedes data synthesis to inform clinical decision making. Standardization is urgently required.[47]

The chronic and relapsing nature of AD and limitations of current therapeutic approaches can be overwhelming for patients and caregivers. By nature of the disease, treatment is multifactorial—encompassing skin hydration and protection and addressing the immunopathology[9,10,17,53,54] (Fig 2). It requires time and commitment on the part of the patient and family.[1,4] The negative effects of AD on quality of life (QoL)—even with treatment—are well documented and include sleep disruption, emotional distress, and effects on productivity and social life.[55] The dollar costs can be substantial (see eCommentary 2 for more information).

Patients with AD often see several specialists to help manage their disease—including primary care clinicians, allergists, and dermatologists.[56] Each might refer to different guidance documents for treating AD—similar, but not necessarily the same.[17] The most recent US guidance documents—*Guidelines of Care for the Management of Atopic Dermatitis* of the American Academy of Dermatology and *Atopic Dermatitis, A Practice Parameter Update 2012* developed by the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology—are directed toward the respective specialists, with some differences between the documents in text, grading of evidence, patient evaluation and severity categorization, and treatment algorithms.[9–11,17,53,57,58] There is a need for a treatment model that can be referred to by all specialties, particularly when it comes to how and when to step up care for the patient.

Approximately two thirds of adults with self-identified eczema report moderate to severe symptoms,[16] and a substantial number of these patients continue to have inadequately controlled disease despite using recommended treatment[59] (Fig 3). The overall proportion of patients with diagnosed moderate to severe AD is not known, although the prevalence in children is estimated to be 33% and increases with age.[12] Data from more than 2,000 patients indicated an average of 136 days annually with acute symptoms—almost 40% of the year. The ability to control symptoms is concerning to patients (and caregivers).[59] The average delay from symptom onset to treatment is 7 days. Refractoriness to topical treatments and multiple medications should be a signal to review and modify treatment in a long-term manner. There is no generalizable time that can be specified, but refractory lesions after the label-recommended duration of treatment (eg, 14 days for superpotent topical corticosteroids) or recurrent clinic visits requiring a step-up in treatment suggest the need to assess maintenance therapy and other factors that might contribute to persistent inflammation. The goal should be to help patients achieve and maintain short- and long-term control of their AD with as few

Table 2
Scoring Systems for Clinician Assessment Used in Clinical Research of Atopic Dermatitis

Scoring system	Description	Severity rating
Validated		
SCORing Atopic Dermatitis (SCORAD)[40–42,46]	3 components: (A) extent—sites affected are shaded on a body drawing and scored by percentage (head and neck 9%; upper and lower limbs 9% each; anterior trunk 18%, back 18%; maximum 100%); (B) intensity score (0 = little or none to 3 = severe) for redness, swelling, crusting or oozing, skin thickening (lichenification), dryness, scratch marks (maximum 18); (C) subjective score (VAS, 0 = none to 10 = worst imaginable) for sleeplessness and itch (maximum 20); SCORAD total score = A/5 + 7B/2 + C (maximum 103)	Mild <25, moderate >25 to <50, severe >50
Eczema Area and Severity Index (EASI)[38,39,41]	2 components: (1) area score (percentage of skin affected) recorded for 4 regions (head and neck; trunk and genitals; upper limbs; lower limbs and buttocks): 0 = none; 1 = 1–9%; 2 = 10–29%; 3 = 30–49%; 4 = 50–69%; 5 = 70–89%; 6 = 90–100%; (2) severity score for each region calculated based on intensity (0 = none to 3 = severe) of redness, thickness or swelling, scratching, lichenification (maximum 12 for each region) Calculation of total regional scores: head and neck: severity score × area score × 0.1 (in children 0–7 y, × 0.2) trunk: severity score × area score × 0.3 upper limbs: severity score × area score × 0.2 lower limbs: severity score × area score × 0.4 (in children 0–7 y, × 0.3) EASI total score = sum of total regional scores (maximum 72)	Mild 1.1–7, moderate 7.1–21, severe 21.1–50, very severe 50.1–72
Patient-Oriented SCORAD (PO-SCORAD)[42,46]	Adaptation of SCORAD for patients and available as an app online (to be shared with the clinician)—similar scoring as SCORAD: extent of affected areas, severity of dry skin outside affected areas, symptom intensity of affected areas, severity of itching, and sleep disturbance; shown to be correlated with SCORAD	Mild <25, moderate >25 to <50, severe >50
Patient-Oriented Eczema Measure (POEM)[41,43]	7 symptoms scored over past week: 0 = no days; 1 = 1–2 d; 2 = 3–4 d; 3 = 5–6 d; 4 = every day (query: Over the last week, on how many days has your skin been itchy, red, bleeding, weeping or oozing clear fluid, cracked, flaking, felt dry or rough because of your eczema?); maximum score 28	Clear or almost clear 0–2, mild 3–7, moderate 8–16, severe 17–24, very severe 25–28
Dermatology Life Quality Index (DLQI)[44,45]	10-question validated questionnaire providing patient's perception of the impact of AD on quality of life in past week; questions include effect of disease and treatment on physical, psychological, and social well-being	Each question is answered according to ratings: 0 = not at all, 1 = a little, 2 = a lot, 3 = very much; maximum 30
Not validated		
Investigator Global Assessment (IGA) score, aka Investigator Static Global Assessment (ISGA) score[47]	FDA categorization of AD severity based on investigator's subjective assessment of a representative lesion according to erythema, induration or papulation, and/or oozing or crusting.	0 = clear to 4 = severe
Six Signs Six Areas Atopic Dermatitis (SASSAD) scale[49,50]	Subjective evaluation of extent of body surface area involved based on 6 signs (erythema, exudation, excoriation, dryness, cracking, lichenification) at each of 6 sites (arms, hands, legs, feet, head and neck, trunk)	Each sign at each site is assessed using a scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe; maximum 108
Three Item Severity (TIS) scale[46,51]	Subjective evaluation of a representative lesion based on erythema, edema or papulation, and excoriation	0 = none to 3 = severe
Pruritus (itch) score[52]	Patient's subjective of itch using a VAS similar to pain scales	VAS: 0 = none to 10 = severe

Abbreviations: AD, atopic dermatitis; FDA, Food and Drug Administration; VAS, visual analog scale.

exacerbations as possible. How to do this is not straightforward. This article describes the AD Yardstick, a practical resource based on the therapeutic utility of recommended strategies for patients when they require a step-up in care. The intent is not to replicate materials in the current guidance documents but to provide updated information summarizing newer data and products that could help clinicians manage AD in their patients for better outcomes.

Figure 3. Some characteristics of moderate to severe atopic dermatitis. (A) Image of a 50-year-old man who has had moderate to severe atopic dermatitis for at least 10 years. In addition to the displayed lesions, he has associated atopic keratoconjunctivitis and is nearly blind in his left eye. Photo courtesy of Luz Fonacier, MD. (B) Image depicts skin atrophy on a patient with a history of severe atopic dermatitis who had used high potency topical corticosteroids to control his symptoms for years. Skin atrophy from topical corticosteroids is a rare but potential side effect of topical corticosteroids. Photo courtesy of Peck Ong, MD. (C) Image of a woman who has numerous excoriations, shown on her legs, and is heavily colonized with *Staphylococcus aureus*. Her pruritus (score 8 of 10) keeps her awake at night. Photo courtesy of Luz Fonacier, MD.

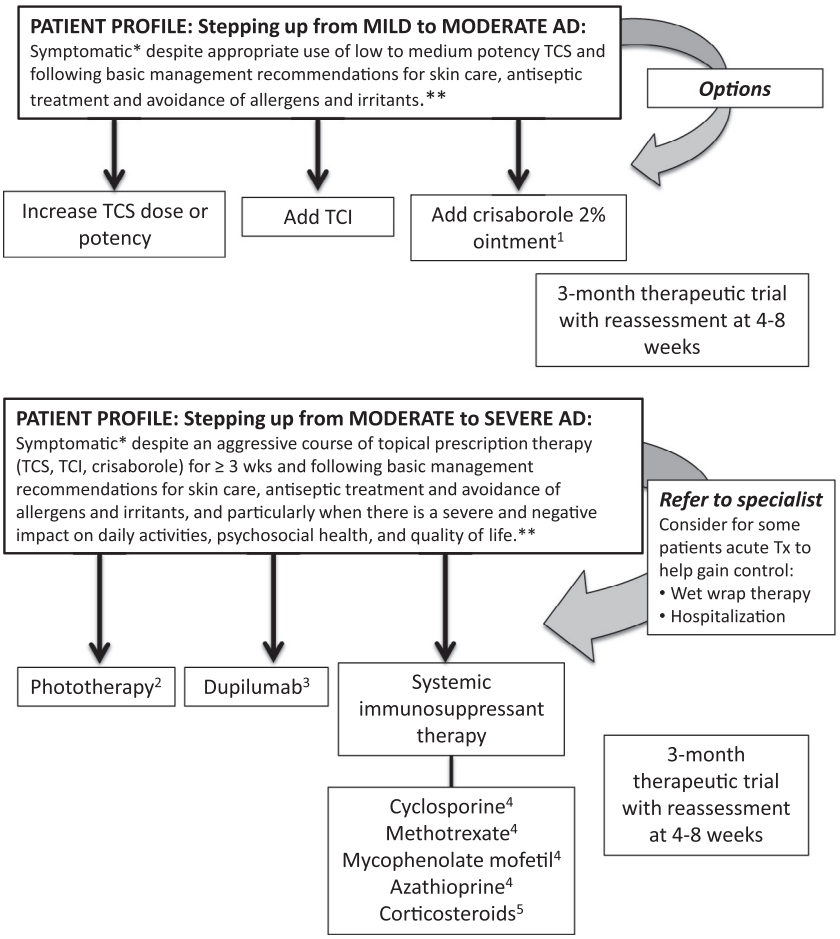

Figure 4. The Atopic Dermatitis Yardstick flow diagram. The patient profiles and recommendations for treatment are based on current guidelines and newer data and the authors' clinical experience as described in the text. *Poorly or inadequately controlled signs and symptoms of atopic dermatitis (AD). **Before stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively affect response to therapy (Table 3). Confirmation is needed that the increased level of symptoms is due to AD. [1]Indicated for patients at least 2 years old with mild to moderate AD.[72] [2]The patient should be willing and able to commit to phototherapy in terms of cost, convenience, and access. [3]Indicated for patients at lest 18 years old with moderate to severe AD.[78] It is the authors' expert opinion that dupilumab has a safety and efficacy profile that is better than that of immunosuppressive agents or phototherapy; cost and coverage are extremely important considerations. Documentation of the patient's disease severity, prior therapies, including failures, and impact on quality of life might be required (Table 5). [4]Not approved by the Food and Drug Administration to treat AD. [5]Approved by the Food and Drug Administration to treat AD but not recommended for long-term maintenance. A short-course of systemic corticosteroids can help resolve severe symptoms, but exacerbation at discontinuation is common. Systemic corticosteroids also can be used as cotreatment during the initiation and optimization of phototherapy, other systemic immunosuppressants, and/or dupilumab. TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

The AD Yardstick (Fig 4) and accompanying text provide patient profiles followed by recommendations and commentary based on current guidance documents and contemporary data on treatment options and the authors' clinical experience. eSupplementary Materials describe the development of the Yardstick and provide relevant background information.

Basic Management of AD

As presented in Figure 2, the management of AD at all levels of severity involves regular maintenance therapy and treatment for exacerbations (ie, flares, acute symptoms). The latter are generally managed with topical anti-inflammatory medications with low to medium potency when the exacerbation is relatively mild and higher potency when the skin appears more inflamed. Discussion of the treatment of AD exacerbations is beyond the scope of this article, and the reader is directed to current guidance documents and review articles.[9,17,58]

The basic management of AD incorporates 3 important nonpharmacologic interventions[9–11,53]:

1. Regular (daily) bathing with warm (but not hot) water hydrates skin and decreases potential skin exacerbating agents—such as bacteria, dirt, crusting, and other irritants. Daily bathing with water alone can substantially decrease AD severity. Of note, a recent systematic review found that the addition of bleach as a disinfectant has not been shown to provide further clinical benefit.[60] The act of bathing can have added benefit, including relaxation.
2. Appropriate application of moisturizer helps maintain adequate hydration of the epidermis, improve barrier function, and decrease transepidermal water loss.[61] Moisturizers are a primary therapy for AD, clinically ameliorating signs and symptoms including erythema, fissuring, and pruritus. By lessening the itch-scratch cycle, an appropriate moisturizer for sensitive skin can decrease the need for topical medications.[62,63] The final choice depends on patient preference, and "generous and frequent" application is recommended, with application soon after bathing to further enhance skin hydration.
3. Avoidance of irritants and allergens specific to the patient's disease and symptoms is important. Common triggering

Table 3
Common Contributors to Loss of Disease Control[1,4,16]

Environmental exposures (eg, allergens, irritants, changes in humidity and temperature)
Comorbid conditions contributing to morbidity (eg, infections, food allergies, contact dermatitis)
Difficulty applying topical medications (eg, "too little, too late")
Poor adherence, which can reflect
Fear of medication adverse effects
Belief that the medication does not help (eg, patients or caregivers reporting that they do not see an immediate effect)
Belief that the medication is not necessary (eg, in relation to regular therapy including basic maintenance treatment—patients or caregivers questioning need for therapy when there are no symptoms or signs of disease)
Belief that treatment is needed only when symptoms and signs of disease become "noticeable"
Inconvenience, including using multiple medications, having to apply topical treatments, need to avoid certain types of clothing and materials, etc
Dislike of provider; distrust of medical establishments
Cost, including lack of insurance or treatment not covered by insurance
Lack of access to health care (eg, phototherapy)
Insufficient medication prescribed

32 irritants include sweat (eg, with excessive exercise or heat), acids, bleaches, fragrances, preservatives, solvents, and wool and heavy, occlusive fabrics. Additional environmental modifications (eg, temperature and humidity control) can help as can using nonirritating liquid laundry soap.

Additional information on bathing, choosing a moisturizer, and trigger avoidance strategies can be found in current guidance documents.[9–11,53] For most patients with mild disease, these interventions are sufficient as maintenance therapy. Continued symptoms despite optimal use of nonpharmacologic interventions suggest the need to evaluate potential barriers to successful care (Table 3) and then, once it is determined that symptoms are due to AD, to step up treatment.[1,4,64]

Step-Up: Mild to Moderate AD

Patient Profile

This section concerns the patient who is symptomatic (eg, poorly or inadequately controlled signs and symptoms of AD) despite appropriate use of low to medium potency topical corticosteroids and following basic management recommendations for skin care, antiseptic treatment, and avoidance of allergens and irritants.

Before stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively affect response to therapy (Table 3). Confirmation is needed that the increased level of symptoms is due to AD.

Commentary

When nonpharmacologic interventions alone are not enough to manage the patient's symptoms, a step-up to maintenance therapy with a topical prescription medication (eg, topical corticosteroid [TCS], topical calcineurin inhibitor [TCI], or crisaborole ointment) should be tried (Fig 4).[9,53,64–67]

Topical corticosteroids and TCIs act on the underlying inflammatory processes and can be used to mitigate active inflammation (treating exacerbations) and prevent relapses (proactive or maintenance therapy).[6,9,53,64] Limitations for these medications relate to potential adverse events with long-term use. Crisaborole 2% topical ointment, the most recent addition to topical agents for treating mild to moderate AD, provides an improved risk-benefit profile that might be appropriate for some patients.[66–70] The following comments reflect the most recent data and the authors' combined clinical experience with these agents.

Topical corticosteroids

Topical corticosteroids are categorized according to potency from class VII (least potent) to class I superpotent (also referred to as "very potent"; eTable 1). Lower potency TCSs are generally recommended for maintenance therapy, although higher potency TCSs can be used in appropriate patients. The choice of agent should consider potency, patient preference, and price.

Multiple dosing recommendations are available. Although twice-daily application of TCSs for up to 4 weeks is commonly recommended for active inflammation, once-daily application might be sufficient for many patients. For long-term maintenance therapy, application once or twice weekly to areas that commonly flare might be appropriate to stop relapse for some patients.[17,53]

Topical corticosteroids can be absorbed through the skin, and although systemic effects are rare, they are not unknown. Use of these agents, particularly higher potency TCSs (eTable 1), is generally discouraged on areas of thin skin, such as the face, neck, and skin folds. Patients should be monitored for local and systemic adverse events as described in the guidelines.[9,53] Patient education delivered in a manner to minimize possible steroid phobia is important. Steroid phobia could be a factor when adherence is not optimal, and if not resolved by information and counseling, then other treatment options should be discussed.

For all patients, the TCS should be used at the lowest effective dose to achieve disease control, and attaining control is the critical factor for this directive. Although the "lowest effective dose" is desired, it is equally important that undertreatment be avoided because that contributes to suboptimal outcomes and patient frustration.[53] All options should be discussed, including long-term TCS and TCI use and more aggressive treatment as needed during exacerbations. Once clearance or near clearance is achieved, consideration should be given to using a lower potency TCS and/or switching to a TCI or crisaborole. Monitoring adherence is critical to successful outcomes.

Pediatric considerations. Topical corticosteroids are used to treat children with AD; those that have specific age indications for pediatric use in the United States are listed in eTable 1. Parents and/or caregivers need to understand the critical role of topical treatment for their child and that adherence to treatment is important for a successful outcome.

Topical calcineurin inhibitors

Topical calcineurin inhibitors—a class of steroid-sparing anti-inflammatory agents that include tacrolimus and pimecrolimus—inhibit calcineurin-dependent T-cell activation, thereby impeding the production of proinflammatory cytokines and mediators.[6,9,17,53,66,71,72]

Like TCSs, dosing recommendations are evolving. Traditionally used at a twice-daily dose for exacerbations and maintenance therapy, recent recommendations suggest once-daily treatment or intermittent treatment 2 to 3 times weekly might be sufficient for ongoing prevention.[9,17,53]

Although often used for their steroid-sparing properties, TCIs are not without adverse effects. These agents have a boxed warning about a possible increased risk of lymphoma, although this has not been proved by clinical experience and studies in the past 15 years.[71,72] Patients and caregivers must be educated to encourage optimal adherence with treatment.[9,17,53]

Pediatric considerations. Pimecrolimus cream and tacrolimus 0.03% ointments are approved for children at least 2 years old.[71,72] Evidence from clinical trials supports the safety and efficacy of

pimecrolimus in infants and children younger than 2 years.[73,74] Tacrolimus 0.1% is indicated for patients older than 15 years.[72] Treatment should follow similar recommendations for use in adults.[53]

Crisaborole: a new agent for mild to moderate AD

Crisaborole 2% topical ointment is a nonsteroidal anti-inflammatory phosphodiesterase 4 (PDE4) inhibitor approved in the United States to treat mild to moderate AD.[67–69,75] Approved by the FDA in 2016, it was the first new topical anti-inflammatory agent indicated for the treatment of AD in over 15 years, developed with the goal of providing patients a topical treatment with an improved risk-benefit profile.

Conversion of the intracellular messenger 3′5′-cyclic adenosine monophosphate into the active metabolite adenosine monophosphate is critical to inflammatory processes, promoting cytokine production. PDE4, one of several enzymes that can mediate the conversion, has been shown to be increased in AD.[69] Inhibiting PDE4 increases cyclic adenosine monophosphate levels and decreases cytokine production. In vitro, crisaborole has been shown to decrease PDE4 levels and inhibit cytokine production from peripheral blood mononuclear cells in a pattern similar to other PDE4 inhibitors and distinct from corticosteroids. Crisaborole also displayed topical anti-inflammatory activity in a skin inflammation model.[67]

Chemically, crisaborole is a unique boron-based compound—a benzoxaborole—and the configuration of boron within the compound enables synthesis of a low-molecular-weight molecule (251 Da) that facilitates the effective penetration of crisaborole through human skin so that it can target PDE4.[67,70] Systemic exposure varies according to the cutaneous surface treated. Crisaborole is rapidly and substantially metabolized to inactive metabolites, limiting continued exposure and systemic PDE4 inhibition.[67,68,70]

The clinical efficacy and safety of crisaborole 2% ointment were established in 2 large, randomized, controlled phase 3 clinical trials in the United States.[67,68] A total of 1,522 subjects (≥2 years old) were included, all with mild to moderate AD at baseline, according to the ISGA score (mild, 2; moderate, 3). Most subjects (≈87%) were children and adolescents (2–17 years old), with approximately 33% 2 to 6 years old. Most subjects (61.6%) had a severity rating of moderate. Use of TCSs or systemic corticosteroids (SCSs) within 28 days and TCIs within 14 days of the trial start was prohibited. Subjects were instructed to apply a layer of study drug to cover each lesion twice daily for 28 days.[67,68]

The primary efficacy variable was an ISGA score of clear or almost clear skin at the end of the 28-day period, with an improvement grade of at least 2 from baseline. Additional outcomes assessed included intensity of pruritus, signs of AD (erythema, exudation, excoriation, induration or papulation, lichenification), and QoL (Dermatology Life Quality Index).[67,68]

In the 2 trials in children and adults, crisaborole 2% ointment ameliorated disease severity as soon as day 8 of treatment; decreased signs and symptoms of AD; and produced rapid and sustained lessening of pruritus.[67,68] These outcomes were significant despite a strong "vehicle effect" relating to the benefits of emollient treatment and placebo response rates that are commonly noted in clinical studies of AD therapies.[68]

The significant decrease in pruritus with crisaborole 2% ointment confirmed previous findings from 2 post hoc pooled analyses of phase 1 and 2 studies, lending support to a possible role for PDE4 in regulating itch through neuronal pathways.[68,70] More data are needed to determine whether crisaborole modulates itch indirectly through anti-inflammatory mechanisms and/or directly through PDE4-induced neuronal inhibition.[68]

Treatment with crisaborole was well tolerated, with similar rates of adverse events reported for patients treated with crisaborole and those treated with vehicle alone. Most adverse events were mild to moderate in severity and considered unrelated or unlikely to be related to treatment. Application site pain (burning, stinging) occurred in at least 1% of patients.[67–70]

Pediatric considerations. Children at least 2 years old were included in clinical trials. Crisaborole was well tolerated.[68,75–77] The pediatric use of crisaborole for children follows similar recommendations to its use in adults.[68,69,75–77]

Incorporating crisaborole into the step-care protocol

Based on safety and efficacy profiles, it has been suggested that TCS be used to treat symptom exacerbations, followed by long-term maintenance therapy with a lower dose of a TCS and/or a TCI or crisaborole. Crisaborole also can be used as a first-line agent in patients averse to using TCS or TCI based on their established adverse event profiles. Of note, crisaborole does not have a boxed warning or any limitations on duration of use. The goal is to proactively prevent relapses, but specific data in support of these treatment regimens are limited: open-label, long-term extension trials of phase 3 studies of crisaborole have been conducted.[69,70,78] It has not been studied for prophylaxis. Which treatment to use as maintenance therapy is a discussion between patients or caregivers and health care providers, taking into consideration patient preferences, risk-benefit profiles, and cost (insurer) factors.[79]

Step-Up: Moderate to Severe AD

Most patients with moderate AD show long-term clinical improvement with moisturizers, avoidance of triggers, and use of prescription anti-inflammatory agents, (eg, TCS, TCI, crisaborole).[17] Patients who do not achieve complete or almost complete resolution of their signs and symptoms might require a step-up (Fig 4). Patients with recalcitrant AD who have persistent and intensely itchy lesions and/or complications with frequent infection should be aggressively managed. Ocular complications and substantial impact on sleep and daily activities also warrant a higher level of treatment.

Patient Profile

This section concerns the patient who is symptomatic (eg, poorly or inadequately controlled signs and symptoms of AD) despite an aggressive course of topical prescription therapy (TCS and/or TCI or crisaborole) for at least 3 weeks and following basic management recommendations for skin care, antiseptic treatment, and avoidance of allergens and irritants. For these patients, AD can have a severe and negative impact on daily activities, psychosocial health, and QoL.

The patient should be willing and able to commit to the treatment chosen, in terms of cost, convenience, access, and adverse events. Before stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively affect response to therapy (Table 3). Confirmation is needed that the increased level of symptoms is due to AD.

Commentary

Treatment options for patients with moderate to severe AD have largely been limited to phototherapy and/or systemic immunosuppressive agents, with the specific step-up determined according to patient need, availability of and access to treatment, and cost.[9,57,80] A new therapeutic approach became available in 2017 with FDA approval of the targeted biological therapy, dupilumab, for patients with moderate to severe AD who have an inadequate response to, or cannot use, topical therapy (Fig 4).[65,81,82]

Table 4
Considerations for Using Phototherapy Treatment for AD[79,82]

Health care system factors	availability of phototherapy and ease of access
	convenience of phototherapy for the patient, particularly proximity to home and/or work
	payer cost and insurance coverage
	out-of-pocket costs, including copays, deductibles, transportation, lost work time, child care, etc
Patient factors	skin type
	history of skin cancer
	history of photosensitive disorder and/or use of photosensitizing medications
	fear of devices and treatment, particularly for children
	location of AD lesions
	AD severity
	baseline disease duration
	persistence

Abbreviation: AD, atopic dermatitis.

Phototherapy

Phototherapy is an option for treating some patients with severe AD. Referral to a center with phototherapy available from a dermatologist with expertise in administering such treatment is recommended.[9,57,80,83] Unfortunately, access to phototherapy is very limited for most patients with AD in the United States. Considerations for treatment are listed in Table 4.

Multiple forms of phototherapy are available. Narrow-band UVB is usually preferred in the United States for long-term or maintenance therapy for chronic AD because of its low-risk profile, relative efficacy, availability, and ease of use for the provider.[9,57,80,84] Phototherapy can be given as monotherapy or in combination with topical treatments or even occasionally with systemic treatments. Short courses of UVA1 can be recommended for exacerbations; and for patients with severe, widespread AD, UVA with psoralen can be tried.[9,57,83,85]

The choice of dosing protocols and frequency of treatment depends on the minimal erythema dose and/or the Fitzpatrick skin type and should be individualized according to the patient's characteristics, history, and symptoms.[57,83] The authors' experience suggests that phototherapy is not optimal for treating severe disease. The reader is directed to current guidance documents by the Joint Task Force and the American Academy of Dermatology for more information about specific protocols.[9,57]

Recent data suggest that the efficacy of phototherapy is multifactorial—reducing inflammatory cells in the skin, decreasing immune markers, reversing epidermal hyperplasia, thickening the stratum corneum, thereby enhancing the protective barrier to entry of external antigens,[9,57,84,86] and decreasing skin bacterial infections, particularly by *Staphylococcus aureus*.[87]

The most common adverse reactions to phototherapy are cutaneous side effects, including actinic damage, local erythema and tenderness, and reversible and irreversible changes in pigmentation. Patients might experience an exacerbation due to excess heat and/or UV exposure. Adverse systemic effects, such as an increased risk for cutaneous malignancies and cataracts, occur less frequently.[9,57,80,83]

Phototherapy involves a time commitment from the patient (and caregiver). The greatest barriers to use in the United States are the lack of access to phototherapy sites and the direct and indirect costs (Table 4). Tanning beds have been suggested as an alternative because of their accessibility, but the increased risk of melanoma and keratinocyte carcinomas should discourage this practice. The potential for home phototherapy under the direction of a physician is a promising option for patients whose access to treatment is limited. However, to date, no studies have examined safety and efficacy outcomes for home therapy in AD.[80,83] More data using better home phototherapy units are needed.

Pediatric considerations. A short course of phototherapy is safe and effective treatment for children with AD unresponsive to topical medications when administered under the care of a specialist physician with expertise in using phototherapy for pediatric AD.[86–88] The duration of a short course of therapy is not well defined and varies between guidances, ranging from several weeks to several months. Treatment duration should be determined according to the clinical outcomes observed for the child. Phototherapy is not approved in the United States for children younger than 12 years, although dermatologists often use it for AD that is recalcitrant to topical medications. The treatment should be individualized according to the needs of the child and family, and concerns and fears should be carefully addressed.[57,87,88]

Systemic immunomodulatory agents

Systemic immunosuppressants are an option for patients whose previous treatments have failed or are considering phototherapy (Fig 4). These include cyclosporine A, methotrexate, mycophenolate mofetil, and azathioprine; all are off-label options in the United States, and data are sparse.[9,17,57,66,89] Systemic corticosteroids (SCSs) are FDA approved to treat inflammatory skin disease (including AD) but are not recommended as maintenance therapy.[9,17,57,89] Therapy with immunomodulatory agents is limited by systemic adverse events; long-term efficacy for these medications has not been demonstrated, and they are not suitable for long-term treatment.

Off-label systemic immunosuppressants. Cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine, although not approved in the United States for the treatment of AD, are used for cases with severe, difficult-to-manage symptoms. A trial of cyclosporine is commonly administered first; if that is not successful, then treatment with the others can be attempted.[9,17,57,66,89] Commonalities in risks and benefits permit some generalizations; considerations for treatment are listed below.[9,17,56,88–90]

- Immunosuppressant medications should be administered under the supervision of an experienced specialist physician.
- There are no consistent recommendations for optimal dosing and duration of therapy or monitoring protocols for any systemic immunosuppressive medication used to treat AD because of the lack of sufficient data.
- Treatment decisions should be based on the patient's AD status, baseline disease duration and persistence, age, medical history, comorbidities, and preferences.
- Treatment is usually initiated with higher doses to gain better control of the disease.
- Once a response is attained and sustained, the immunosuppressive drug should be adjusted to the minimal dose effective for the patient. Other therapies (eg, TCS, TCI) can be continued to titrate the immunomodulatory agent to the lowest dose and duration needed. With clearance or near clearance of disease, the drug should be tapered and, if possible, discontinued. If tapering is not successful, then phototherapy and/or dupilumab can be used.
- Appropriate blood test monitoring is needed for adverse events and/or to adjust dosages.
- The decision to start systemic immunosuppressants in children should be evaluated on a case-by-case basis.

Other potential systemic agents (eg, interferon-γ, intravenous immunoglobulin, rituximab, oral calcineurin inhibitors) are beyond the scope of this article. Data for these are limited, and evidence supporting their use in AD is insufficient.

Systemic corticosteroids. The anti-inflammatory effects of a short course (2–3 weeks) of parenteral or oral corticosteroids could help

some patients with intermittent, severe, recalcitrant AD. However, rebound is often seen, and these agents should be used with extreme caution and in special circumstances. Efficacy is based largely on clinical experience because data are limited, but case reports suggest that short-term SCS use could be useful for the rapid control of severe and relapsing symptoms and for some patients during initiation and/or optimization of phototherapy or other systemic immunosuppressant therapy.[57,66,89] Long-term use of SCS or frequent high-dose bursts (eg, intramuscular injections) should be avoided because of the possibility of serious systemic adverse events. The potential risks and benefits of treatment should be carefully weighed for each patient.[9,57,66,89]

If a long-term course of SCS is initiated, or if the patient has had frequent short courses of SCS, monitoring for adverse events, including hypothalamic-pituitary-adrenal axis suppression, is advised. Children and adolescents might show decreased linear growth while being treated.[9,57]

Once clearance or near clearance of disease is achieved, the dose of SCS should be tapered and, if possible, discontinued. An increased risk of exacerbation during tapering can be avoided by aggressive cotreatment with topical anti-inflammatory therapy.[9,57] Other treatments (eg, topical anti-inflammatory agents, phototherapy, systemic immunosuppressants, dupilumab) should be considered to maintain remission.

Dupilumab (Interleukin-4 and Interleukin-13 Antagonism)

Dupilumab is a fully human monoclonal antibody targeting the common α-chain of the interleukin (IL)-4 and IL-13 receptor, thereby blocking signaling through the 2 T_H2 cytokines.[91] Increased levels of IL-4 and IL-13 in AD lesions contribute to the epidermal pathology by inhibiting epidermal cell differentiation and synthesis of lipids and antimicrobial peptides.[5,6,8,91] Dupilumab received FDA approval in March 2017 for adult patients with moderate to severe AD who had an inadequate response to, or could not use, topical therapy.[81] It is an option for patients whose previous treatments have failed or are considering systemic immunosuppressants or phototherapy.

In phase 1, 2, and 3 trials, dupilumab showed robust clinical improvement of AD[5,65,91–94] (Fig 5). Two phase 3 trials showed significantly greater improvement in Eczema Area and Severity Index score (≥75%) from baseline to week 16 in dupilumab-treated patients compared with placebo.[93] Dupilumab also decreased skin inflammation and reversed epidermal-associated measures.[82,91,92,94] Treatment with dupilumab was associated with major improvements in AD-associated symptoms, including pruritus and anxiety and depression.

In these trials, dupilumab exhibited an excellent safety profile, with headache, nasopharyngitis, injection-site reactions, and conjunctivitis being more frequent in the drug group, with a trend for decreased skin infections in dupilumab- vs placebo-treated patients.[82,91,94] A 52-week efficacy and safety study of dupilumab added to medium potency TCS in adults with moderate to severe AD showed similar clinical benefits over placebo as the 16-week studies and a comparable safety profile.[95]

Dupilumab is self-administered as a subcutaneous injection with an initial adult dose of 600 mg (2 × 300 mg/2-mL prefilled syringes) followed by a single 300-mg injection given every 2 weeks.[81] There are currently no data for stepping down or discontinuation once efficacy has been attained.

Pediatric considerations. Studies in children and adolescents are ongoing.

Incorporating dupilumab into the step-care protocol

Dupilumab is the first FDA-approved biologic therapy for the treatment of moderate to severe AD in adults. It has the potential to alleviate the signs and symptoms of the disease and to lessen the impact of the disease on QoL for patients with extensive and often recalcitrant disease (Fig 5).

Figure 5. Images of 2 patients with severe atopic dermatitis before and after 16 weeks of treatment with dupilumab in phase 2 and 3 trials. These patients had chronic, recalcitrant disease for many years and treatment with topical and systemic agents, including cyclosporine A and oral prednisone, had failed. These patients continue to be treated with dupilumab. Photos courtesy of Emma Guttman-Yassky, MD, PhD.

Dupilumab could reorder the current protocol for treating moderate to severe AD, with the prospect of providing patients a safe therapeutic option for long-term control. Based on phase 2 and 3 studies, dupilumab can be the next step in treatment after topical therapy for these patients. Pediatric data will be important, and postmarketing clinical experience is needed to evaluate long-term efficacy and side effects. With new data and expanded clinical experience, the status of dupilumab in treatment protocols can change. It is the authors' expert opinion that dupilumab has a safety and efficacy profile that is better than that of immunosuppressive agents or phototherapy; cost and coverage are extremely important considerations.[79] Documentation of the patient's disease severity, prior therapies, including failures, and impact on QoL might be required (Table 5).

Table 5
Practical Pearls for Prescribing Dupilumab

1. Document diagnosis of AD (not just eczema); see Table 1
2. Qualify and document severity of AD as mild, moderate, or severe based on involved body surface area and/or other measures; see Table 2
3. Provide supporting description in physical examination; see descriptions in EASI and SCORAD in Table 2
4. Address prior therapies and/or therapeutic failures, including why the patient is not a candidate for other specific therapy
5. Be specific when describing a therapeutic failure, which is defined as ≥1 of the following:
   Inadequate response to medium-to-high potency topical therapy
   Suboptimal clinical improvement
   Failure to achieve stable long-term control (eg, frequent exacerbations)
   Unacceptable adverse events
6. Review the insurance requirements of the formulary because some insurers might require specific documentation and severity measurements (eg, use of EASI, positive determination that signs and symptoms are due to AD and not complicating factors such as parasitic infections, etc)

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; SCORAD, SCORing Atopic Dermatitis.

Other treatments

Wet dressings and short-term hospitalizations are other options for patients with severe, recalcitrant AD whose multiple therapies have failed.[9,53,54,96–98] These treatments also are sometimes used for patients for whom treatment choices are limited due to costs and/or insurer considerations. More information is provided in current guidance documents and several excellent reviews.[9,53,54,96–98]

Targeting Allergy

For some patients with an allergic phenotype and positive allergy test reaction, a trial of allergen immunotherapy or the anti–immunoglobulin E (IgE) therapy, omalizumab, can be attempted. However, the data for these 2 options are weak.

Allergen-Specific Immunotherapy

Allergen-specific immunotherapy, sublingual or subcutaneous, is currently not a recommended treatment for AD but remains a topic of discussion and study.[99–102] A trial can be considered for some patients with a positive allergen test (eg, skin prick test, specific IgE) reaction and a history of AD symptoms being triggered by exposure to that allergen. In particular, the Atopic Dermatitis Practice Parameter Update states that the clinician might consider immunotherapy in selected patients with AD and aeroallergen sensitivity, but the data for this option are of limited quality.[99–102] Most case reports and published studies have described outcomes in patients with documented house dust mite, birch, or grass pollen sensitivities. Sublingual immunotherapy has been studied as an option for patients with milder disease[58,102]; subcutaneous immunotherapy has shown better results than sublingual immunotherapy for patients with more severe symptoms, particularly those with house dust mite sensitivity.[10,58,101] Nine to 12 months of treatment might be required to see clinical benefit.[58]

Omalizumab

Omalizumab, an anti-IgE monoclonal antibody, was first approved to treat patients with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. It subsequently showed efficacy in patients with chronic idiopathic urticaria.[103] Limited data exist for patients with AD and results were variable.[104,105] A recent systematic review of 26 studies with variable patient numbers (total N = 174), study designs, and dosing protocols reported insufficient evidence to support using omalizumab to treat AD. However, physician assessments indicated that 50% of patients had a good or excellent response to omalizumab, 12.5% had a moderate response, and 37.5% had no response or deterioration.[105] The results suggest that omalizumab could be an option for some patients with severe, recalcitrant AD, but the relevance of IgE in the expression of AD can vary across patient phenotypes. IgE might not be an ideal treatment target in AD.

Discussion

This initial iteration of the AD Yardstick focuses on the evolving therapeutic paradigm with the introduction of the first new approved treatments for AD in the United States in 15 years—crisaborole 2% topical ointment, indicated for treating patients at least 2 years old with mild to moderate AD,[75] and dupilumab injection, indicated for the treatment of patients at least 18 years old with moderate to severe AD.[81] These medications (and others in development) have the potential to change the protocols for managing AD but are constrained at this time by cost, comfort with traditional care, and, in some cases, insurer's requirements (eg, failed trials of other therapies). The authors believe this will change with more experience, and health care professionals need to better understand how and when to incorporate the newer therapies (including others to be approved) into evolving protocols. The authors' expert opinions have been captured in the text of the AD Yardstick and accompanying flow diagram (Fig 4), while recognizing these limitations.

Because AD is a chronic condition with a complex pathology, a positive response to therapy could require frequent evaluations. Patients who do not respond to treatment (eg, frequent exacerbations, poor long-term disease control) should be reassessed, first to ensure that the lack of response is due to the disease (Table 3) and then to step up treatment.[9–11,18,106] With the AD Yardstick, the authors have tried to provide a practical flow for step-up recommendations, particularly for patients with greater disease severity. As for other chronic diseases, these are the patients who are least likely to have a sustained step change in treatment and at the same time be a major driver of overall costs to the health care system.[107]

For the patients with severe, recalcitrant AD, treatment is not inexpensive. Many do not see a specialist until late in the disease progression, resulting in undertreatment that can aggravate the loss of disease control.[16,59] The association of poor disease control with infection, general health problems, and development or exacerbation of comorbid conditions adds to the financial burden.[1,3,108–110] Equally important is the significant negative impact of poor disease control on QoL—skin pain, loss of sleep, loss of the ability to concentrate and be productive at work and school, and loss of self-confidence and participation in normal daily activities have been documented.[1,37,55,59,108,111,112] Addressing the psychosocial and behavioral aspects of this chronic, pruritic disease can be critical.[113]

Focusing on the patients with the moderate to severe level of AD, the new biologic therapy, dupilumab, provides hope. Indeed, its fast-track approval by the FDA acknowledges its life-altering potential. These patients are so severely affected by their symptoms—burning itch; dry, irritated skin; unsightly lesions; frequent infections (Fig 5)—that they cannot sleep or perform normal daily activities; for some, isolation becomes a refuge. Treatment in clinical trials has made a difference—not only for their skin but also in the ability to have a normal day.[5,91,94,112] Currently, access to dupilumab is variable according to the patient's insurer. Specific documentation of severity and need is usually required. Table 5 presents the authors' recommendations to help document the patient's need for dupilumab.

Regardless of severity, the early identification and aggressive treatment of AD is a critical first step to improving outcomes. Patients

and clinicians might need to become more adept at identifying poorly controlled AD and recognizing the need for a sustained step-up in maintenance therapy. Patients (and caregivers) should have an action plan to follow. The early recognition of symptoms is particularly important for infants and young children because AD and the subsequent atopic march present mostly in those age groups (eCommentary 1) and, for some, primary and secondary prevention strategies could decrease the development of other atopic conditions.[110,114] Research into an effective prevention strategy for AD and associated allergic conditions has not yet provided a consistent paradigm, although pilot studies suggest that for infants at high risk of AD, daily full-body emollient therapy from birth could be preventive.[115,116]

In summary, there is a need for a treatment model that can be referred to by all specialties, particularly when it comes to how and when to step up care for the patient. The AD Yardstick provides a practical resource, based on current evidence and clinical experience, to help realign treatment to the evolving therapeutic paradigm, particularly for patients not responsive to current standards of care. Which treatment to use as maintenance therapy is a discussion between patients or caregivers and health care providers, taking into consideration patient age, previous treatment failures, lesion location, patient and caregiver preferences and lifestyle, risk-benefit profiles, and cost (insurer) factors. An aggressive treatment strategy, such as proposed by the AD Yardstick, can lessen the burden of the disease—to the patient and family and to the health care system.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2017.10.039.

References

[1] Drucker AM. Atopic dermatitis: burden of illness, quality of life, and associated complications. *Allergy Asthma Proc*. 2017;38:3–8.
[2] Bieber T. Atopic dermatitis. *Ann Dermatol*. 2010;22:125–137.
[3] 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.
[4] Silverberg JI. Health care utilization, patient costs, and access to care in us adults with eczema: a population-based study. *JAMA Dermatol*. 2015;151:743–752.
[5] Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol*. 2017;139:S65–S76.
[6] Guttman-Yassky E, Krueger JG, Lebwohl MG. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. *Exp Dermatol*. 2017;doi:10.1111/exd.13336. [published online ahead of print March 7, 2017].
[7] Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387:1109–1122.
[8] Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol*. 2003;112(suppl):S118–S127.
[9] Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131:295–299.
[10] Boguniewicz M. Atopic dermatitis: the updated practice parameter and beyond. *Allergy Asthma Proc*. 2014;35:429–434.
[11] Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70:338–351.
[12] Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis*. 2014;25:107–114.
[13] Margolis JS, Abuabara K, Bilker W, et al. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatol*. 2014;150:593–600.
[14] 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.
[15] Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol*. 2013;132:1132–1138.
[16] Hanifin JM, Reed ML, Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. *Dermatitis*. 2007;18:82–91.
[17] Eichenfield LF, Ahluwalia J, Waldman A, et al. Current guidelines for the evaluation and management of atopic dermatitis: a comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology guidelines. *J Allergy Clin Immunol*. 2017;139:S49–S57.
[18] Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol*. 2014;134:769–779.
[19] Czarnowicki T, Esaki H, Gonzalez J, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)1 TH2/TH1 cell imbalance, whereas adults acquire CLA1 TH22/TC22 cell subsets. *J Allergy Clin Immunol*. 2015;136:941–951.
[20] Czarnowicki T, Malajian D, Shemer A, et al. Skin-homing and systemic T-cell subsets show higher activation in atopic dermatitis versus psoriasis. *J Allergy Clin Immunol*. 2015;136:208–211.
[21] Czarnowicki T, Gonzalez J, Bonifacio KM, et al. Diverse activation and differentiation of multiple B-cell subsets in patients with atopic dermatitis but not in patients with psoriasis. *J Allergy Clin Immunol*. 2016;137:118–129.
[22] Czarnowicki T, Gonzalez J, Shemer A, et al. Severe atopic dermatitis is characterized by selective expansion of circulating TH2/TC2 and TH22/TC22, but not TH17/TC17, cells within the skin-homing T-cell population. *J Allergy Clin Immunol*. 2015;136:104–115.
[23] Czarnowicki T, Esaki H, Gonzalez J, et al. Alterations in B-cell subsets in pediatric patients with early atopic dermatitis. *J Allergy Clin Immunol*. 2017;140:134–144.
[24] Esaki H, Brunner PM, Renert-Yuval Y, et al. Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. *J Allergy Clin Immunol*. 2016;138:1639–1651.
[25] Esaki H, Czarnowicki T, Gonzalez J, et al. Accelerated T-cell activation and differentiation of polar subsets characterizes early atopic dermatitis development. *J Allergy Clin Immunol*. 2016;138:1473–1477.
[26] Noda S, Suarez-Farinas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol*. 2015;136:1254–1264.
[27] Noda S, Krueeger JG, Guttman-Yassky E. The translational revolution and use of biologics in patients with inflammatory skin diseases. *J Allergy Clin Immunol*. 2015;135:324–336.
[28] Mannucci C, Casciaro M, Minciullo PL, et al. Involvement of microRNAs in skin disorders: a literature review. *Allergy Asthma Proc*. 2017;38:9–15.
[29] Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: end of the drought. *J Allergy Clin Immunol*. 2017;140:633–643.
[30] Guttman-Yassky E, Dhingra N, Leung DYM. New era of biological therapeutics in atopic dermatitis. *Expert Opin Biol Ther*. 2013;13:549–561.
[31] Ungar B, Garcet S, Gonzalez J, et al. An integrated model of atopic dermatitis biomarkers highlights the systemic nature of the disease. *J Invest Dermatol*. 2017;137:603–613.
[32] Schmitt J, Langan S, Deckert S, et al. Harmonising Outcome Measures for Atopic Dermatitis (HOME) initiative. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. *J Allergy Clin Immunol*. 2013;132:1337–1347.
[33] Czarnowicki T, Kreuger JG, Guttman-Yassky E. Skin barrier and immune dysregulation in atopic dermatitis: an evolving story with important clinical implications. *J Allergy Clin Immunol Pract*. 2014;2:371–379.
[34] Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol*. 2016;51:329–337.
[35] Sun D, Ong PY. Infectious complications in atopic dermatitis. *Immunol Allergy Clin North Am*. 2017;37:75–93.
[36] Malajian D, Guttman-Yassky E. New pathogenic and therapeutic paradgms in atopic dermatitis. *Cytokine*. 2015;73:311–318.
[37] Narla S, Silverberg JI. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. *Ann Allergy Asthma Immunol*. 2018;120:66–72.
[38] Hanifin JM, Thurston M, Omoto M, et al. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. 2001;10:11–18.
[39] Leshem YA, Hajar T, Hanifin JM, et al. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol*. 2015;172:1353–1357.
[40] Kunz B, Oranje AP, Labreze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1997;195:10–19.
[41] Schram ME, Leeflang MM, Lindeboom R, et al. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. *Allergy*. 2012;67:99–106.
[42] Stalder JF, Barbarot S, Wollenberg A, et al. PO-SCORAD Investigators Group. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy*. 2011;66:1114–1121.
[43] Charman C, Venn A, Williams HC. The Patient-Oriented Eczema Measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol*. 2004;140:1513–1519.
[44] Finlay AY, Khan GK. Dermatology Life Quality Index—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19:210–216.
[45] Hongbo Y, Thomas CL, Harrison MA, et al. Translating the science of quality of life into practice: what do Dermatology Life Quality Index scores mean? *J Invest Dermatol*. 2005;125:659–664.
[46] Oranje AP, Glazenburg EJ, Wolkerstorfer A, et al. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol*. 2007;157:645–648.

[47] Futamura M, Leshem YA, Thomas KS, et al. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: many options, no standards. *J Am Acad Dermatol*. 2016;74:288–294.
[48] Charman CR, Venn AJ, Williams HC. Measurement of body surface area involvement in atopic eczema. An impossible task? *Br J Dermatol*. 1999;140:109–111.
[49] Berth-Jones J. Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. *Br J Dermatol*. 1996;135(suppl 48):25–30.
[50] Charman CR, Venn AJ, Williams HC. Reliability testing of the Six Area, Six Sign Atopic Dermatitis severity score. *Br J Dermatol*. 2002;146:1057–1060.
[51] Wolkerstorfer A, De Waard van der Spek FB, Glazenburg EJ, et al. Scoring the severity of atopic dermatitis: three item severity score as a rough system for daily practice and as a pre-screening tool for studies. *Acta Derm Venereol*. 1999;79:356–359.
[52] Yarbrough KB, Neuhaus KJ, Simpson EL. The effects of treatment on itch in atopic dermatitis. *Dermatol Ther*. 2013;26:110–119.
[53] 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.
[54] Izadi N, Leung DYM. Clinical approach to the patient with refractory atopic dermatitis. *Ann Allergy Asthma Immunol*. 2018;120:23–33.
[55] Eckert L, Gupta S, Amand C, et al. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: an analysis using the National Health and Wellness Survey. *J Am Acad Dermatol*. 2017;77:274–279.
[56] Saavedra JM, Boguniewicz M, Chamlin S, et al. Patterns of clinical management of atopic dermatitis in infants and toddlers: a survey of three physician specialties in the United States. *J Pediatr*. 2013;163:1747–1753.
[57] Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71:327–349.
[58] 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.
[59] Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol*. 2006;118:226–232.
[60] Chopra R, Vakharia PP, Sacotte R, et al. Efficacy of bleach baths in reducing severity of atopic dermatitis: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol*. 2017;119:435–440.
[61] Czarnowicki T, Malajian D, Khattri S, et al. Petrolatum: barrier repair and antimicrobial responses underlying this "inert" moisturizer. *J Allergy Clin Immunol*. 2016;137:1091–1102.
[62] Lindh JD, Bradley M. Clinical Effectiveness of moisturizers in atopic dermatitis and related disorders: a systematic review. *Am J Clin Dermatol*. 2015;16:341–359.
[63] Van Zuuren EJ, Fedorowicz Z, Arents BWM. Emollients and moisturisers for eczema: abridged Cochrane systematic review including GRADE assessments. *Br J Dermatol*. 2017;doi:10.1111/bjd.15602. [published online ahead of print April 22, 2017].
[64] Brunner PM, Khattri S, Garcet S, et al. A mild topical steroid leads to progressive antiinflammatory effects in the skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol*. 2016;138:169–178.
[65] Guttman-Yassky E, Ungar B, Malik K, et al. Molecular signatures order the potency of topically applied anti-inflammatory drugs in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2017;140:1032–1042, e13.
[66] Silverberg JI. Atopic dermatitis treatment: current state of the art and emerging therapies. *Allergy Asthma Proc*. 2017;38:243–249.
[67] Jarnagin K, Chanda S, Coronado D, et al. Crisaborole topical ointment, 2%: a nonsteroidal, topical, anti-inflammatory phosphodiesterase 4 inhibitor in clinical development for the treatment of atopic dermatitis. *J Drugs Dermatol*. 2016;15:390–396.
[68] 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.
[69] Crisaborole (Eucrisa) for atopic dermatitis. *Med Lett Drugs Ther*. 2017;59:34–35.
[70] Zane LT, Chanda S, Jarnagin K, et al. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. *Immunotherapy*. 2016;8:853–866.
[71] Elidel® (pimecrolimus) cream, 1% [prescribing information]. Laval, QC, Canada: Valeant Pharmaceuticals International; June 2017.
[72] Protopic® (tacrolimus) ointment 0.03%, ointment 0.1% [prescribing information]. Madison, NJ: LEO Pharma; November 2016.
[73] Luger T, Boguniewicz M, Carr W, et al. Pimecrolimus in atopic dermatitis: consensus on safety and the need to allow use in infants. *Pediatr Allergy Immunol*. 2015;26:306–315.
[74] Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics*. 2015;135:597–606.
[75] Eucrisa™ (crisaborole) ointment 2%, for topical use [prescribing information]. Palo Alto, CA: Anacor Pharmaceuticals; December 2016.
[76] 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;33:380–387.
[77] Tom WL, Van Syoc M, Chanda S, et al. Pharmacokinetic profile, safety, and tolerability of crisaborole topical ointment, 2% in adolescents with atopic dermatitis: an open-label phase 2a study. *Pediatr Dermatol*. 2016;33:150–159.
[78] Hebert AA, Spellman M, Stein Gold LF, et al. Long-term safety of crisaborole topical ointment, 2% in children and adults with mild to moderate atopic dermatitis. *J Am Acad Dermatol*. 2017;77:641–649.
[79] Institute for Clinical and Economic Review. Dupilumab and crisaborole for atopic dermatitis: effectiveness and value. Final evidence report and meeting summary. June 8, 2017.
[80] Rodenbeck DL, Silverberg JI, Silverberg NB. Phototherapy for atopic dermatitis. *Clin Dermatol*. 2016;34:607–613.
[81] Dupixent® (dupilumab) injection, for subcutaneous use [prescribing information]. Bridgewater, NJ: Regeneron Pharmaceuticals, Sanofi-Aventis US, LLC; March 2017.
[82] Hamilton JD, Ungar B, Guttman-Yassky E. Drug evaluation review: dupilumab in atopic dermatitis. *Immunotherapy*. 2015;7:1043–1058.
[83] Patrizi A, Raone B, Ravaioli GM. Management of atopic dermatitis: safety and efficacy of phototherapy. *Clin Cosmet Investig Dermatol*. 2015;8:511–520.
[84] Tintle S, Shemer A, Suarez-Farinas M, et al. Reversal of atopic dermatitis with narrowband UVB phototherapy and biomarkers for therapeutic response. *J Allergy Clin Immunol*. 2011;128:583–593, e1-4.
[85] Bogaczewicz J, Malinowska K, Sysa-Jedrzejowska A, et al. Medium dose ultraviolet A1 phototherapy and mRNA expression of interleukin 8, interferon γ, and chemokine receptor 4 in acute skin lesions in atopic dermatitis. *Postepy Dermatol Alergol*. 2016;33:170–175.
[86] Silva SH, Guedes AC, Gontijo B, et al. Influence of narrow-band UVB phototherapy on cutaneous microbiota of children with atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2006;20:1114–1120.
[87] Clayton TH, Clark SM, Turner D, et al. The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. *Clin Exp Dermatol*. 2007;32:28–33.
[88] Eustace K, Dolman S, Alsharqui A, et al. Use of phototherapy in children. *Pediatr Dermatol*. 2017;34:150–155.
[89] Roekevisch E, Spuls PI, Kuester D, et al. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *J Allergy Clin Immunol*. 2014;133:429–438.
[90] Wollenberg A, Oranje A, Deleuran M, et al. ETFAD/EADV eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol*. 2016;30:729–747.
[91] Hamilton JD, Suarez-Farina M, Dhingra N, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol*. 2014;134:1293–1300.
[92] Beck LA, Thaci D, Hamilton JD, et al. Dupilimab treatment in adults with moderate-tosevere atopic dermatitis. *N Engl J Med*. 2014;371:130–139.
[93] Thaci D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet*. 2016;387:40–52.
[94] 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.
[95] Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebocontrolled, phase 3 trial. *Lancet*. 2017;389:2287–2303.
[96] Nicol NH, Boguniewicz M, Strand M, et al. Wet wrap therapy in children with moderate to severe atopic dermatitis in a multidisciplinary treatment program. *J Allergy Clin Immunol Pract*. 2014;2:400–406.
[97] Gittler JK, Wang JF, Orlow SJ. Bathing and associated treatments in atopic dermatitis. *Am J Clin Dermatol*. 2017;18:45–57.
[98] Dabade TS, Davis DM, Wetter DA, et al. Wet dressing therapy in conjunction with topical corticosteroids is effective for rapid control of severe pediatric atopic dermatitis: experience with 218 patients over 30 years at Mayo Clinic. *J Am Acad Dermatol*. 2012;67:100–106.
[99] Tam H, Calderon MA, Manikam L, et al. Specific allergen immunotherapy for the treatment of atopic eczema. *Cochrane Database Syst Rev*. 2016;(2):CD008774.
[100] Slavyanakaya TQ, Derkach VV, Sepiashivili RI. Debates in allergy medicine: specific immunotherapy efficiency in children with atopic dermatitis. *World Allergy Organ J*. 2016;9:15.
[101] Ginsberg DN, Eichenfield L. Debates in allergy medicine: specific immunotherapy in children with atopic dermatitis, the "con" view. *World Allergy Organ J*. 2016;9:16.
[102] Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. *Ann Allergy Asthma Immunol*. 2017;118:276–282.
[103] Xolair® (omalizumab) for injection, for subcutaneous use [prescribing information]. San Francisco, CA: Genentech USA; East Hnover, NJ: Novartis Pharmaceuticals; June 2017.

[104] Wang H-H, Li Y-C, Huang Y-C. Efficacy of omalizumab in patients with atopic dermatitis: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2016; 138:1719–1722.
[105] Holm JG, Agner T, Sand C, et al. Omalizumab for atopic dermatitis: case series and a systematic review of the literature. *Int J Dermatol*. 2017;56:18–26.
[106] Leung DYM, Guttman-Yassky E. Assessing the current treatment of atopic dermatitis: unmet needs. *J Allergy Clin Immunol*. 2017;139:S49–S57.
[107] Chipps BE, Corren J, Israel E, et al. Asthma yardstick: practical recommendations for a sustained step-up in asthma therapy for poorly controlled asthma. *Ann Allergy Asthma Immunol*. 2017;118:133–142.
[108] Filanovsky MG, Pootongkam S, Tamburro JE, et al. The financial and emotional impact of atopic dermatitis on children and their families. *J Pediatr*. 2016; 169:284–290, e5.
[109] Brunner PM, Silverberg JI, Guttman-Yassky E, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol*. 2017; 137:18–25.
[110] Czarnowicki T, Kreuger JG, 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.
[111] Vakharia PP, Chopra R, Sacotte R, et al. Burden of skin pain in atopic dermatitis. *Ann Allergy Asthma Immunol*. 2017;119:548–552.
[112] Simpson EL, Bieber T, Eckert L, et al. Patient burden of moderate to severe atopic dermatitis (AD): insights from a phase 2b clinical trial of dupilumab in adults. *J Am Acad Dermatol*. 2016;74:491–498.
[113] Klinnert MD, Booster G, Copeland M, et al. Role of behavioral health in management of atopic dermatitis. *Ann Allergy Asthma Immunol*. 2018;120:42–48.
[114] Egawa G, Kabashima K. Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic march. *J Allergy Clin Immunol*. 2016;138:350–358.
[115] Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134:818–823.
[116] Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014; 134:824–830.

Supplementary Data

eMethods

Theauthors worked in teams to review the evidence for current treatment options (approved and not approved by the FDA) as identified by the most recent guidance documents[1–6] and according to the type of step-up (mild to moderate, moderate to severe). The wording in the text reflects the severity classification of the step-care scheme as developed by the authors and shown in Figure 2. Differences are noted from other reported severity classifications such as those used in the clinical trials for approval of crisaborole and dupilumab.

Recommendations for adult patients (≥18 years of age) were reviewed and pediatric considerations were added where appropriate. Newer data and potential treatment options not yet described in the guidelines also were evaluated. The evidence was not graded, except as graded for the guidance documents. Patient profiles were created as practical points of reference for the reader, and the associated flow diagram (Fig 4) provides the authors' concept for a "best practice summary" of the available strategies for increasing and/or modifying therapy according to the patient's severity and disease control. All authors reviewed and provided appropriate revisions to the report in development, and all gave written approval to the final document. It is anticipated that, like the guidance documents, the AD Yardstick will be updated on a regular basis according to new research findings.

eCommentary 1. AD Immunopathology

Because of its association with atopic manifestations, the pathogenesis of AD was traditionally believed to be based on IgE, and approximately 80% of patients with AD show increased levels of serum IgE.[7,8] More recent data suggest that epidermal barrier defects and T_H2- and T_H22-deviated immune reactions might be the critical factors for disease onset.[8–12] Genetic mutations affecting the function of a key epidermal barrier protein, filaggrin, underlie barrier disruption and dehydration of the epidermis.[9,10,13] The barrier disruption increases permeability of the epidermis to external allergens and irritants and induces release of thymic stromal lymphopoietin, which triggers immune activation of T_H2 and T_H22 pathways. The T_H2 cytokines IL-4 and IL-13 stimulate B cells to produce IgE antibodies to allergens, and these cytokines in addition to IL-22 are strong suppressors of barrier protein (eg, filaggrin, loricrin) expression, creating a cycle of barrier disruption and immune activation as illustrated in Figure 1.[8–14] Thymic stromal lymphopoietin and T_H2-derived IL-31 also contribute to pruritus, and scratching for relief can exacerbate the skin barrier breakdown.[8,9,11] AD also is associated with changes in the epidermal microbiome related to decreased

eTable 1
Potency Classification of Topical Corticosteroids Used to Treat Atopic Dermatitis[1,4]

Class	Corticosteroid	Formulations	Approved for pediatric use
I. Very high potency or superpotent	Betamethasone dipropionate 0.05%	Cream, ointment	
	Clobetasol propionate 0.05%	Cream, ointment	
	Diflorasone diacetate 0.05%	Ointment	
	Halobetasol propionate 0.05%	Cream, ointment	
II. High potency	Amcinonide 0.1%	Ointment	
	Betamethasone dipropionate 0.05%	Cream, ointment	
	Desoximetasone 0.25%	Cream, gel, ointment	
	Diflorasone diacetate 0.05%	Ointment	
	Fluocinonide 0.05%	Cream, gel, ointment, solution	
	Halcinonide 0.1%	Cream	
	Mometasone furoate 0.1%	Ointment	≥2 y old
III. Medium to high potency	Amcinonide 0.1%	Cream, lotion	
	Betamethasone dipropionate 0.05%	Cream	
	Betamethasone valerate 0.1%	Ointment	
	Desoximetasone 0.05%	Cream	
	Diflorasone diacetate 0.05%	Cream	
	Fluocinonide 0.05%	Cream	
	Fluticasone propionate 0.005%	Ointment	
	Halcinonide 0.1%	Ointment, solution	
	Triamcinolone acetonide 0.1%	Ointment	
IV. Medium potency	Hydrocortisone valerate 0.2%	Ointment	
	Flurandrenolide 0.05%	Ointment	
	Fluocinolone acetonide 0.025%	Ointment	
	Mometasone furoate 0.1%	Cream	≥2 y old
	Triamcinolone acetonide 0.1%	Cream	
V. Medium to low potency	Betamethasone dipropionate 0.05%	Lotion	
	Betamethasone valerate 0.1%	Cream	
	Fluticasone acetonide 0.025%	Cream	
	Fluticasone propionate 0.05%	Cream	≥3 mo old
	Flurandrenolide 0.05%	Cream	
	Hydrocortisone valerate 0.2%	Cream	
	Prednicarbate 0.1%	Cream	≥1 y old
VI. Low potency	Alclometasone dipropionate 0.05%	Cream, ointment	
	Betamethasone valerate 0.05%	Lotion	
	Desonide 0.05%	Gel, foam	≥3 mo old
	Fluocinolone acetonide 0.01%	Cream, oil, solution	oil, ≥3 mo old
	Triamcinolone acetonide 0.1%	Cream	
VII. Lowest potency	Hydrocortisone hydrochloride 1%	Cream, ointment	≥2 y old
	Hydrocortisone hydrochloride 2.5%	Cream, lotion, ointment	
	Hydrocortisone acetate 1%	Cream, ointment	≥2 y old
	Hydrocortisone acetate 2.5%	Cream, lotion, ointment	
	Pramoxine hydrochloride 1.0%	Cream, lotion, ointment	
	Pramoxine hydrochloride 2.5%	Cream, lotion, ointment	

production of antimicrobial peptides and increased risk of infection, particularly with *Staphylococcus aureus*.[9,11,15–17] For more information, the reader is directed to several excellent review articles.[8–14,18,19]

Atopic dermatitis is associated with the development of other atopic conditions such as asthma and rhinosinusitis.[1–3,19–24] This "atopic march" is beyond the scope of this article but could be related to systemic immune abnormalities in AD and inflammatory processes secondary to epidermal barrier disruption extending to the respiratory epithelium.[25–28] For more information, the reader is directed to current guidance documents and review articles.[1–3,19–26,28,29]

eCommentary 2. Burden of AD

The negative effects of AD on quality of life—even with treatment—are well documented and include sleep disruption, emotional distress, and effects on productivity and social life. These can relate to the severe itching, scratching, and skin pain of AD or reflect embarrassment about the appearance of lesional skin and negative feelings about the time-consuming nature of treatment.[29–35] Positive associations have been reported between AD and attention-deficit/hyperactivity disorder,[29,36,37] anxiety disorders,[29,30,35,38] and depression,[29,30,39] especially in patients with AD and sleep loss.[37,38,40] Caretakers can be affected. The development of other atopic conditions such as asthma and rhinosinusitis that commonly develop after the onset of AD can further frustrate the patient and family.[1–3,20–23]

The costs of AD in dollars and time (eg, taking care of skin, seeing the physician for assessment and monitoring) also can overwhelm patients and their families. Older estimates have placed the direct cost burden in the United States at approximately $3.8 billion a year,[41] with direct medical expenditures in 2005 estimated at more than $1 billion.[42] A 2011 survey of 79 families of children with AD in Cleveland, Ohio reported average personal costs of $274/month.[43] All are likely underestimates because of the difficulty in identifying the total direct and indirect expenses and the increasing prevalence of AD and increasing health care costs.[29]

eReferences

[1] Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131:295–299.
[2] Boguniewicz M. Atopic dermatitis: the updated practice parameter and beyond. *Allergy Asthma Proc*. 2014;35:429–434.
[3] Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70:338–351.
[4] 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.
[5] Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71:327–349.
[6] 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.
[7] Martel BC, Litman T, Hald A, et al. Distinct molecular signatures of mild extrinsic and intrinsic atopic dermatitis. *Exp Dermatol*. 2016;25:453e9.
[8] Furue M, Chiba T, Tsujo G, et al. Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies. *Allergol Int*. 2017;66:398–403.
[9] Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol*. 2017;139:S65–S76.
[10] Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol*. 2014;134:769–779.
[11] Brunner PM, Leung DYM, Guttman-Yassky E. Immunologic, microbial, and epithelial interactions in atopic dermatitis. *Ann Allergy Asthma Immunol*. 2018;120:34–41.
[12] Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: end of the drought. *J Allergy Clin Immunol*. 2017;140:633–643.
[13] McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *J Allergy Clin Immunol*. 2013;131:280–291.
[14] Noda S, Krueeger JG, Guttman-Yassky E. The translational revolution and use of biologics in patients with inflammatory skin diseases. *J Allergy Clin Immunol*. 2015;135:324–336.
[15] Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol*. 2016;51:329–337.
[16] Sun D, Ong PY. Infectious complications in atopic dermatitis. *Immunol Allergy Clin North Am*. 2017;37:75–93.
[17] Narla S, Silverberg JI. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. *Ann Allergy Asthma Immunol*. 2018;120:66–72.
[18] Guttman-Yassky E, Krueger JG, Lebwohl MG. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. *Exp Dermatol*. 2017;doi:10.1111/exd.13336. [published online ahead of print March 7, 2017].
[19] Ungar B, Garcet S, Gonzalez J, et al. An integrated model of atopic dermatitis biomarkers highlights the systemic nature of the disease. *J Invest Dermatol*. 2017;137:603–613.
[20] Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol*. 2003;112(suppl):S118–S127.
[21] Egawa G, Kabashima K. Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic march. *J Allergy Clin Immunol*. 2016;138:350–358.
[22] Brunner PM, Silverberg JI, Guttman-Yassky E, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol*. 2017;137:18–25.
[23] Marenholz I, Nickel R, Ruschendorf F, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol*. 2006;118:866–871.
[24] Saunders SP, Moran T, Floudas A, et al. Spontaneous atopic dermatitis is mediated by innate immunity, with the secondary lung inflammation of the atopic march requiring adaptive immunity. *J Allergy Clin Immunol*. 2016;137:482–491.
[25] Czarnowicki T, Esaki H, Gonzalez J, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)[1] TH2/TH1 cell imbalance, whereas adults acquire CLA[1] TH22/TC22 cell subsets. *J Allergy Clin Immunol*. 2015;136:941–951.
[26] Czarnowicki T, Esaki H, Gonzalez J, et al. Alterations in B-cell subsets in pediatric patients with early atopic dermatitis. *J Allergy Clin Immunol*. 2017;140:134–144.
[27] Esaki H, Brunner PM, Renert-Yuval Y, et al. Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. *J Allergy Clin Immunol*. 2016;138:1639–1651.
[28] Esaki H, Czarnowicki T, Gonzalez J, et al. Accelerated T-cell activation and differentiation of polar subsets characterizes early atopic dermatitis development. *J Allergy Clin Immunol*. 2016;138:1473–1477.
[29] Drucker AM. Atopic dermatitis: burden of illness, quality of life, and associated complications. *Allergy Asthma Proc*. 2017;38:3–8.
[30] Eckert L, Gupta S, Amand C, et al. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: an analysis using the National Health and Wellness Survey. *J Am Acad Dermatol*. 2017;77:274–279.
[31] Margolis JS, Abuabara K, Bilker W, et al. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatol*. 2014;150:593–600.
[32] 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.
[33] Vakharia PP, Chopra R, Sacotte R, et al. Burden of skin pain in atopic dermatitis. *Ann Allergy Asthma Immunol*. 2017;119:548–552.
[34] Silverberg JI, Garg NK, Paller AS, et al. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol*. 2015;135:56–66.
[35] Garg N, Silverberg JI. Association between childhood allergic disease, psychological comorbidity, and injury requiring medical attention. *Ann Allergy Asthma Immunol*. 2014;112:525–532.
[36] Strom MA, Fishbein AB, Paller AS, et al. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. *Br J Dermatol*. 2016;175:920–929.
[37] Romanos M, Gerlach M, Warnke A, et al. Association of attention-deficit/ hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health*. 2010;64:269–273.
[38] Dalgard FJ, Gieler U, Tomas-Aragones L, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological outpatients in 13 European countries. *J Invest Dermatol*. 2015;135:984–991.
[39] Yu SH, Silverberg JI. Association between atopic dermatitis and depression in US adults. *J Invest Dermatol*. 2015;135:3183–3186.
[40] Schmitt J, Chen CM, Apfelbacher C, et al. Infant eczema, infant sleeping problems, and mental health at 10 years of age: the prospective birth cohort study LISAplus. *Allergy*. 2011;66:404–411.
[41] Ellis CN, Drake LA, Prendergast MM, et al. Cost of atopic dermatitis and eczema in the United States. *J Am Acad Dermatol*. 2002;46:361–370.
[42] Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55:490–500.
[43] Filanovsky MG, Pootongkam S, Tamburro JE, et al. The financial and emotional impact of atopic dermatitis on children and their families. *J Pediatr*. 2016;169:284–290, e5.