Special Article

Expert Perspectives on Management of Moderate-to-Severe Atopic Dermatitis: A Multidisciplinary Consensus Addressing Current and Emerging Therapies

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Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease that affects children and adults. Until recently, the only Food and Drug Administration–approved systemic treatment option for patients with moderate-to-severe AD was systemic steroids, which are not recommended by current guidelines and are commonly associated with disease

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Abbreviations used
AAD- American Academy of Dermatology
AD- Atopic dermatitis
BSA- Body surface area
EASI- Eczema Area and Severity Index
FDA- Food and Drug Administration
QOL- Quality of life
SC- Steering committee
TCS- Topical corticosteroid
UV- Ultraviolet

rebound. Instead, clinicians choose from several off-label immunosuppressants, which can have serious adverse effects. A significant number of these patients go untreated. Research on the immunopathogenesis of AD has paved the way for new, targeted, systemic therapies for moderate-to-severe AD. In early 2017, the Food and Drug Administration approved dupilumab for adults with moderate-to-severe AD whose disease is not adequately controlled with topical therapies. Although the national guidelines can be very helpful to clinicians, the process for updating them does not allow for timely incorporation of novel therapies. A steering committee of AD experts, including dermatologists, allergists, and a patient advocacy group representative, developed recommendations on the basis of a literature review and expert opinion to help clinicians understand how new therapies fit into the current treatment paradigm and to provide practical recommendations for assessing AD severity, treatment response, and treatment failure. **© 2017 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).** **(J Allergy Clin Immunol Pract 2017;■:■-■)**

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Skin disease represents a major global health burden. In the Global Burden of Disease Study 2013, skin diseases were the fourth largest cause of disability worldwide; dermatitis was the most burdensome skin disease.[1] Atopic dermatitis (AD) is a chronic, relapsing, pruritic, and inflammatory skin disease often associated with elevated serum IgE levels that commonly occurs alongside type I allergies, asthma, and allergic rhinitis.[2] AD has primarily been considered a pediatric disease, with up to 90% developing their first symptoms by age 5 years.[3,4] In the 2007 National Survey of Children's Health, with more than 91,000 children surveyed, approximately 13% of children younger than 18 years in the United States had AD.[5] However, AD also affects a significant number of adults either as persistent disease from childhood or as adult-onset or recurrent AD.[6-8] The prevalence of AD among adults ranges from 7% to 10%.[9,10]

Many patients with AD can achieve disease control with good skin care habits and topical treatments.[11] However, these treatments often have inadequate efficacy in patients with moderate-to-severe AD. Until recently, the only Food and Drug Administration (FDA)-approved treatment for moderate-to-severe AD was systemic corticosteroids. Although offering higher efficacy than topical treatments, systemic corticosteroids are not recommended by treatment guidelines because of short- and long-term side effects and patients often rebound after discontinuing treatment.[11] Other options include phototherapy, which may not be available or practical in all settings, and various immunosuppressants, none of which is approved for AD in the United States, and many of which have the potential for serious adverse effects. Patients with moderate-to-severe AD are often given topical treatments before or in conjunction with a systemic treatment or as maintenance therapy after tapering off systemic treatment.[11] The lack of safe and effective systemic treatments means that most patients with moderate-to-severe AD are not well controlled.[12]

Although primarily affecting the skin, AD is increasingly being recognized as a systemic disease with atopic as well as nonatopic comorbidities, with important implications for management and treatment.[13-16] The nonlesional skin of patients with moderate-to-severe AD shows extensive immune and barrier abnormalities, reflecting the systemic nature of the disease.[14,17] In addition, AD is associated with an increased risk of infections,[5,10,18] neuropsychiatric disorders,[19-22] cancer,[23-26] and possibly cardiovascular disease.[27,28] Although some of these relationships remain controversial and complicated by the effects of AD treatment,[29] they nonetheless highlight the increasing burden of this disease and the need for a more systemic approach to establish safe and effective therapies that target its complex pathophysiology.

Recent insights into the immune pathogenesis of AD, including a greater understanding of the role of T_H2 cytokines, have led to translational opportunities in targeted therapies, such as biologics, ushering in a new era for the treatment of moderate-to-severe AD. In particular, several mAbs are being investigated for AD that target key cytokines involved in inflammation.[30]

Given the advent of new treatment modalities for AD and the recent approval of the first biologic for moderate-to-severe AD, there is an urgent need to develop evidence-based, practical recommendations to support allergists and dermatologists in selecting appropriate treatment for patients with moderate-to-severe AD. At present, the process of updating the American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma & Immunology Joint Task Force Practice Parameter and the American Academy of Dermatology (AAD) guidelines do not allow for timely incorporation of novel therapies into these guidance documents. The goal of this expert panel was to develop consensus recommendations relating to the diagnosis and treatment of patients with moderate-to-severe AD in the era of biologic therapies, on the basis of a critical review of the literature and expert opinion. Similar initiatives and expert consensus reports have been published when new anti—vascular endothelial growth factor therapies became available for the treatment of retinal vein occlusion,[31] on the use of biologics in moderate-to-severe psoriasis,[32] and on optimizing treatment of systemic and biologic therapy for moderate-to-severe psoriasis.[33] The panel did not receive compensation for writing this publication.

METHODS

This initiative comprised several steps outlined in Figure 1.

In July 2016, a steering committee (SC) consisting of a multidisciplinary group of AD experts, including 8 dermatologists, 2 allergists, and a patient advocacy group representative, met to identify and prioritize a number of essential questions concerning

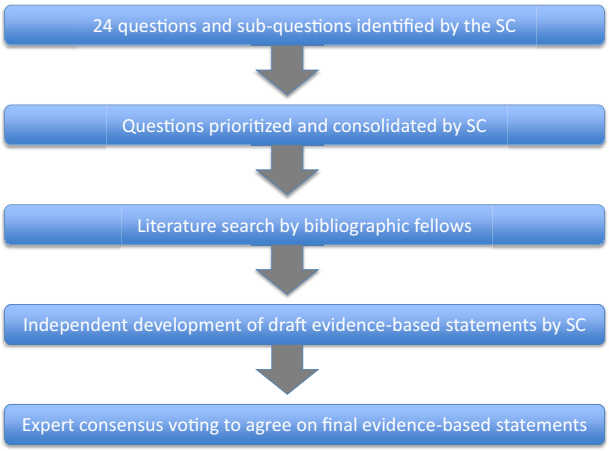

FIGURE 1. The initiative consisted of several steps, starting with the identification of key questions in July 2016 and ending with consensus voting on evidence-based statements in January 2017.

the evaluation and management of moderate-to-severe AD in the era of biologic therapies. These included both contextual questions relating to the definition and diagnosis of AD and practical questions relating to the definition of AD severity and the potential role of emerging biologics in the treatment of moderate-to-severe AD (Table I). Adverse events and contraindications to specific systemic treatments were also reviewed.

Once the questions were prioritized, medical students, research fellows, and residents were selected as bibliographic fellows to conduct a structured, rapid review of the literature to address each question. The literature review was divided among 10 fellows, each of whom was mentored by at least 2 SC members. Search strings were developed, tested, and refined. Fellows searched databases, including Medline, the Cochrane Library, the Global Resource for EczemA Trials database, Excerpta Medica dataBASE, and Web of Science. They also reviewed abstracts presented at key congresses, such as the American Academy of Dermatology and the European Academy of Dermatology and Venereology, starting in 2014.

Relevant articles were screened in 2 stages. In stage 1, titles and abstracts were screened independently by 2 fellows to identify potentially useful articles. All articles identified by either fellow were included in the full list for review and were then retrieved and screened in stage 2. Relevant articles were assigned a level of evidence in stage 2, in accordance with Strength of Recommendation Taxonomy or the Newcastle-Ottawa Scale scales, depending on subject matter.

A summary report of the evidence addressing each question was produced by the fellows and independently reviewed by each SC member. Expert perspectives from each member of the SC were collated to construct draft statements to answer each question.

The SC discussed, refined, and voted on the draft statements during 2 remote and 1 live voting round. Consensus was evaluated via a modified Delphi methodology.[34] During each round of voting, each member of the SC anonymously voted on each set of statements/recommendations using a 9-point scale (1 = strong disagreement; 9 = strong agreement). During the second round of voting, 1 SC member, who was not present at the consensus conference, voted postmeeting on the revised statements. The final round of voting took place in January 2017 to refine SC recommendations on 2 questions. The patient advocacy group representative voted only on those questions for which she felt qualified to contribute from a patient perspective.

TABLE I. Questions identified by the SC

Definition and diagnosis of AD (contextual questions)
1. What is the definition of atopic dermatitis?
2. What is the difference between atopic dermatitis and other types of eczema?
3. How should atopic dermatitis be diagnosed and how should diagnosis be documented?
4. Is atopic dermatitis a systemic disease?
Definition of moderate-to-severe AD in clinical practice
5. How should moderate-to-severe atopic dermatitis be defined in clinical practice?
How should BSA and site of involvement be considered in the assessment of atopic dermatitis severity?
In localized disease, do certain affected areas (eg, high-impact or visible areas) modify the classification of disease severity?
Role of emerging biologics in the management of moderate-to-severe AD
6. What is the definition of treatment failure in atopic dermatitis?
What is the optimal length of a trial with any treatment before an inadequate response can be considered as treatment failure?
Are there biomarkers in the blood or skin that would predict response to treatment?
7. What is the optimal role of conventional systemic treatments in the treatment of moderate-to-severe atopic dermatitis?
What is the optimal duration of treatment with conventional systemic therapies, considering safety concerns?
For how long is it safe to continue cyclosporine treatment in a responding patient?
8. What is the appropriate pathway that should be followed before a patient is eligible for biologic treatment?
Should biologic treatment be recommended as first-line systemic treatment in all patients with moderate-to-severe atopic dermatitis who are uncontrolled with topical therapies, or is a trial of phototherapy or conventional systemic (ie, cyclosporine, methotrexate, azathioprine, phototherapy, systemic corticosteroids) therapy required?
What is the role of biologic therapy in atopic dermatitis patients who are currently well controlled with conventional systemic therapy?

For each set of statements, consensus was considered achieved if 75% or more of the AD experts voted within the 7 to 9 range on the 9-point scale. Each statement/recommendation was assigned a strength score (ie, the median score) and a level of consensus, defined as the percentage of votes with a score of 7 to 9.

RESULTS

In total, 4711 references were retrieved during the literature search; 234 of these were included in the summary evidence report.

Definition and diagnosis of AD

The SC agreed upon a concise, yet complete definition of AD based on current consensus statements and guidelines, which is presented in Table II.[2,35-40] All the definitions examined included chronicity or relapsing course and pruritus. Various definitions included inflammation or inflammatory disease, prevalence in children, family or personal history of allergic

TABLE II. Recommendations for defining and diagnosing AD

Recommendation	Voting results	
	Strength of recommendation*	Level of consensus†
Definition of AD (N = 11)‡ 1. AD is a chronic, relapsing, noncontagious, pruritic inflammatory skin disease that occurs more commonly in children, but also affects many adults and has an age-specific typical morphology and distribution. It is often associated with elevated serum IgE levels and a personal or family history of allergic conditions such as allergic rhinoconjunctivitis, asthma, or food allergies. 2. The clinical findings that define AD may be divided into essential features, important features seen in most cases, and associated features that help to suggest the diagnosis of AD (Table III). 3. The diagnosis of AD should not be excluded in individuals lacking evidence of allergen sensitization.	9	100
Differentiating between AD and other types of eczema (N = 10)‡ 1. Other forms of eczematous dermatitis may occur concomitantly or independently. The pattern or distribution of the dermatitis, together with historical features, may alert one to an allergic or irritant contact dermatitis, seborrheic dermatitis, chronic vesicular hand dermatitis (dyshidrotic eczema), or nummular dermatitis. Eczematous dermatitis may be a feature of genetic or immunodeficiency disorders and nutritional deficiency. Other differential diagnoses of concern include eczematous drug eruptions, cutaneous T-cell lymphoma (particularly in adults), and scabies.	9	100
Diagnosing AD (N = 11)‡ 1. There is a need for simple, validated diagnostic criteria for AD suitable for use in daily practice. 2. The Hanifin-Rajka criteria for diagnosing AD are suitable for use in clinical trials. 3. The UK Working Party's diagnostic criteria for AD (UK criteria) are suitable for use in clinical trials and population-based studies. 4. Diagnosis of AD should be documented showing criteria used, key morphological and/or molecular characteristics, and features used to ascertain severity of disease.	9	100
The systemic nature of AD (N = 10)‡ 1. AD is characterized by cutaneous and systemic inflammation. − There is evidence of nonlesional immune activation in patients with moderate-to-severe disease. 2. AD is strongly associated with extracutaneous allergic disease, such as asthma, allergic rhinoconjunctivitis, and food allergy. 3. Infections are increased in patients with AD. 4. AD has a significant association with multiple neuropsychiatric comorbidities, attention deficit/hyperactivity disorder, depression, anxiety, and sleep disorders. 5. Patients with AD may be at increased risk for coronary artery disease, ischemic stroke, and other cardiovascular disease. 6. AD places patients at a higher risk for lymphoma; this association may be linked with the use of steroids in therapy.	8.5	100

*Median score on a 1-9 scale.

†Percentage of votes with a score of 7-9 on a 9-point scale.

‡Number of the 11 SC members who voted. The patient advocate representative voted only on those questions for which she felt qualified to contribute from a patient perspective.

disorders or asthma, and a specific morphology and/or distribution.

The SC's definition stresses the chronic and relapsing nature of AD and although including elevated serum IgE levels, it does not require this feature for diagnosis. The definition also acknowledges that AD frequently occurs in conjunction with other allergic conditions. The clinical findings first outlined by the AAD and divided into "essential," "important," and "associated" features were deemed useful for clinicians (Table III).[35]

AD as a systemic disease. AD is increasingly being recognized as a systemic disease that has important therapeutic implications. Patients with AD have signs of systemic inflammation, including systemic T-cell activation, which corresponds to higher IL-13 and IL-22 levels and lower IFN-γ levels compared with controls.[41] In addition, patients with AD have a high proportion of chronically activated memory B cells, which favor differentiation into plasma cells, producing much higher levels of antibodies.[42]

AD is also strongly associated with extracutaneous manifestations and comorbidities. Patients with AD often develop other atopic diseases, such as asthma, food allergy, allergic rhinitis, and allergic conjunctivitis.

There is consistent evidence that patients with AD are at increased risk for lymphoma, squamous cell carcinoma, and basal cell carcinoma.[23-26] However, a case-control study within a national registry (N = 13,687) found that the increased risk of lymphoma was correlated with length of treatment with topical corticosteroids (TCSs) (odds ratio, 3.21; $P < .05$), highlighting the need to disentangle the effects of disease and treatment on cancer risk.[29]

In a retrospective, longitudinal cohort study of 21,756 subjects, AD occurring before age 3 years increased the risk of autism spectrum disorder by more than 3-fold and the risk of attention deficit/hyperactivity disorder nearly 2-fold.[19] In addition, increased rates of depression, anxiety, somatization, and injury requiring medical attention have been observed in multiple case-control studies.[19-22]

TABLE III. Essential, important, and associated features that define AD

Essential features include:	Important features include:	Associated features include:

• Pruritus
• Eczematous dermatitis (acute, subacute, chronic reaction patterns)
  ○ Typical morphology and age-specific patterns often occur:
  ■ Facial, neck, and extensor involvement in infants and children
  ■ Sparing of the groin and axillary regions in infants and children
  ■ Flexural lesions at any age
• Chronic or relapsing history
	• Early age of onset
	• Atopy
	  ○ Personal and/or family history of atopic disorders
	  ○ Raised total IgE levels or allergen-specific IgE
	• Xerosis (dry skin)
	• Lichenification
		• Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
		• Ocular/periorbital changes
		• Other regional findings (eg, nipple involvement, eyelid involvement, perioral changes, periauricular lesions)
		• Perifollicular accentuation/lichenoid lesions in patients of color
		• Lichen simplex chronicus/prurigo nodularis
		• Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)

Finally, patients with AD are at increased risk for certain cutaneous infections thought to be mediated in part by the compromised skin barrier function. These classically include *Staphylococcus aureus*, herpesvirus, and coxsackievirus. However, there is also an association with human papillomavirus (warts), dental caries, otitis media, upper and lower respiratory tract infections, and urinary tract infections.[5,10,18]

Differentiating AD from other forms of eczema. One factor complicating the diagnosis of AD is differentiating it from other forms of eczema, such as irritant contact dermatitis, seborrheic dermatitis, chronic vesicular hand dermatitis (dyshidrotic eczema), and nummular dermatitis. Eczema represents a "reaction pattern" or family of pruritic inflammatory dermatoses that present with a range of characteristic morphological features associated with acute, subacute, and chronic stages. These include irritant and allergic contact dermatitis and AD, which have similar histology, including epidermal spongiosis and a perivascular lymphocytic infiltrate. These diseases may require different treatments and determining which disease is present is crucial. In addition, a single patient can manifest multiple types of eczema.[43] The SC recommends clinical assessments, including the pattern and distribution of skin lesions as well as historical features to accurately diagnose AD. In general, biopsies may be needed to rule out cutaneous T-cell lymphoma, psoriasis, and other diseases. Other analyses, such as immune studies, may be informative to rule out immunodeficiencies with eczema, including Netherton syndrome, Wiskott-Aldrich syndrome, hyper-IgE syndrome, DOCK8 immunodeficiency, severe combined immunodeficiency disease, and Omenn syndrome, among others,[44-47] especially in infants and children.

Diagnosing and documenting AD in clinical practice. Given the complications surrounding the definition and diagnosis of AD, there is a need for clear, practical, and validated diagnostic criteria. The Hanifin and Rajka criteria[48] are often recommended because of their completeness and are considered the criterion standard for AD diagnosis. Although they are often used in clinical trials, they are cumbersome in clinical practice. Furthermore, the validity of several of the minor criteria has been questioned.[2] Two subsequent criteria were developed as simpler, less cumbersome alternatives to the Hanifin and Rajka criteria: the UK working party diagnostic criteria for AD (UK criteria)[49-51] and the AAD consensus criteria.[35] Both these criteria have been used in clinical trials; however, the AAD criteria have not been validated or compared with other diagnostic criteria, and the UK criteria have been validated only in hospital and population-based settings. Only 1 set of criteria, the Millennium Criteria, has been validated in a clinical setting[52,53]; however, these criteria divide AD into phenotypic AD, characterized by negative allergen-specific IgE testing, and AD. Many of the guidelines, including those by the AAD,[2] the European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma, and Immunology PRACTALL consensus,[36] and the Association of the Scientific Medical Societies Germany,[37] do not make this distinction. Therefore, the SC does not recommend using the Millennium Criteria, regardless of the setting. The SC agreed that there is a need for simple, validated diagnostic criteria for AD suitable for daily use in clinical practice.

The literature search did not reveal any AD-specific information on how to document AD diagnosis. However, documentation of AD is important, as demonstrated in a questionnaire-based study that was only 43% sensitive when adult patients were asked whether they had ever been diagnosed with eczema compared with a diagnosis of AD at that visit. The SC recommends that clinicians document the diagnostic criteria used (Table II), any key morphological and/or molecular characteristics (Table III), and features used to ascertain disease severity (Table IV).

Definition of moderate-to-severe AD in clinical practice

Current disease severity scoring systems. The literature review revealed 62 distinct severity scoring measures and 28 quality-of-life (QOL) tools used in AD clinical research. Only 3 of these scales, the Scoring Atopic Dermatitis, Eczema Area and Severity Index (EASI) (including assessments of the severity of AD signs), and Patient-Oriented Eczema Measure (patient-reported assessment of the frequency of AD symptoms), have been adequately validated.[2,54] These measures are primarily designed for the research setting and are not practical for routine use in clinical practice.[2] In addition, there are no validated biomarkers for disease severity. Total serum IgE level is the most frequently studied biomarker; however, a recent meta-analysis showed only a moderate correlation between IgE levels and disease severity.[55] The SC concluded that IgE is *not* a reliable biomarker of AD and

TABLE IV. Recommendations for defining moderate-to-severe AD and determining disease severity in clinical practice

Recommendation	Voting results	
	Strength of recommendation*	Level of consensus†
Definition of moderate-to-severe AD (N = 11)‡	9	100
1. Moderate-to-severe AD may be considered when 1 or more of the following features are present: – A minimum involvement of 10% BSA – Regardless of BSA: • Individual lesions with moderate-to severe-features • Involvement of highly visible areas or those important for function (eg, neck, face, genitals, palms, and/or soles) • Significantly impaired QOL		
2. Current disease severity scales and QOL scales, although validated for use in clinical trials, are not practical for routine utilization in clinical practice.		
3. Although global assessment scores have not been validated in office settings, it is simple to classify disease as "clear," "almost clear," "mild," "moderate," or "severe."		
4. Clinicians should actively assess the impact of disease on QOL during clinic visits (ie, sleep, pruritus, and impact on activities of daily living, and work).		
5. No biomarkers, including serum IgE, are currently recommended for assessment of disease severity.		

*Median score on a 1-9 scale.
†Percentage of votes with a score of 7-9 on a 9-point scale.
‡Number of the 11 SC members who voted. The patient advocate representative voted only on those questions for which she felt qualified to contribute from a patient perspective.

does not recommend using IgE to determine or monitor disease severity.

In response to a need for high-quality outcome measures in AD, the Harmonizing Outcomes Measures for Eczema initiative recently developed 4 core AD outcome domains for use in clinical research to facilitate intertrial comparison: clinical signs measured by using a physician-assessed instrument, symptoms measured using a patient-assessed instrument, health-related QOL, and long-term flare control.[56,57] There is a similar need to delineate clear, practical definitions and severity measures for AD in the clinical setting.

Considerations for defining moderate-to-severe AD. Given the lack of disease severity scoring systems for clinical settings, the SC proposed a definition of moderate-to-severe AD (Table IV) that takes into account body surface area (BSA) involvement, lesional features and locations, and disease impact on QOL. The SC recommends that moderate-to-severe AD be diagnosed when BSA involvement is more than 10%. The method of calculating BSA varies between disease severity scoring systems. EASI estimates BSA using body choice bands, while Scoring Atopic Dermatitis uses the "rule of nines," a chart that divides the body into sections representing 9% BSA, using the rater's palm. Using palm size as a measure of BSA may lead to underestimating or overestimating the diseased area.[54] A recent systematic review revealed that the most consistent method across age and race is to equate the adult palm without fingers as 0.5% total BSA.[58]

BSA is not the only determining factor when defining moderate-to-severe AD. Lesion features and location as well as the effect of the disease on QOL should also be considered. These factors are often interrelated. For example, facial AD is associated with lower QOL than is AD on the rest of the body.[59] In addition, pruritus has a significant impact on QOL and contributes to inflammation and superinfection. In patients with localized disease, pruritus location can contribute to the disease's effect on QOL.[2] Other key considerations for QOL include sleep quality, emotional and mental health disturbance, and interference with daily activities. In patients of color, dyspigmentation as a long-term sequela of AD can adversely affect the QOL impact of the disease.[60] The effect of AD on QOL can be judged as mild, moderate, or severe, on the basis of clinician's judgment of the above factors and those listed in Table IV.

Determining response to treatment and defining treatment failure

Determining response to treatment. There are no validated biomarkers to monitor treatment response in patients with AD. As noted above, serum IgE levels are not indicative of AD disease severity, and should not be used to assess treatment response or failure. Several biomarkers, including thymus and activation-regulated chemokine (CCL17), cutaneous T-cell attracting chemokine (CCL27), E-selectin, eosinophil cationic protein, lactate dehydrogenase, and macrophage-derived chemoattractant (CCL22) are being studied for their ability to predict disease severity or treatment response. Several of these biomarkers, including thymus and activation-regulated chemokine, cutaneous T-cell attracting chemokine, E-selectin, and macrophage-derived chemoattractant, are involved in recruiting inflammatory cells to the skin. Although some studies have shown correlations between the levels of these markers and disease severity or treatment response, the data are often inconsistent, and their use in clinical practice cannot be recommended at this time.[55,61-63]

Defining treatment failure. There is currently no standard definition of treatment failure in AD. The SC has proposed 4 types of treatment failure, presented in Table V, which patients with AD may experience:

- Inadequate clinical improvement: Although patients may experience a minor clinical improvement following treatment, this is insufficient to infer that treatment has been successful.

TABLE V. Recommendations for determining response to treatment and treatment failure in AD

Recommendation	Voting results	
	Strength of recommendation*	Level of consensus†
Definition of treatment failure (N = 11)‡	9	100
1. There are no accepted criteria for defining treatment failure in AD.		
2. Treatment failure, despite appropriate dose and duration of and adherence to a therapeutic agent, may be defined by 1 or more of the following:		
– Inadequate clinical improvement		
– Failure to achieve stable long-term disease control		
– Presence of ongoing impairment (eg, pruritus, pain, loss of sleep, and poor quality of life) while on treatment		
– Unacceptable adverse events or poor tolerability experienced with the treatment		
Time to treatment failure (N = 11)‡	7	80
3. Although there is no generalizable time to demonstrate the efficacy of topical treatments (TCSs and topical calcineurin inhibitors), given the range of potency and dosage forms of steroids, the recommended regimen for topical treatment use is up to 4 wk at a time for active treatment and 2-3 times weekly application at sites prone to recurrence for preventative treatment. In selected patients and specific body sites, treatment for longer than 4 wk may be necessary.		
Biomarkers (N = 11)‡	9	100
4. There are currently no acceptable biomarkers that would predict response to treatment.		

*Median score on a 1-9 scale.
†Percentage of votes with a score of 7-9 on a 9-point scale.
‡Number of the 11 SC members who voted. The patient advocate representative voted only on those questions for which she felt qualified to contribute from a patient perspective.

- Failure to achieve stable long-term disease control: This includes the occurrence of flares, regardless of severity, disease duration, or short-term treatment with corticosteroids.
- Failure to relieve impairment: Because effect on QOL is an important factor for AD treatment, failure to improve QOL measures should be considered treatment failure.
- Unacceptable adverse events: An unacceptable safety profile that leads to treatment discontinuation should be considered treatment failure.

Treatment resistance has been defined as a lack of response to therapeutic agents despite complete compliance to the prescribed regimen. Those in whom treatment resistance is suspected should be completely reassessed to ensure that the diagnosis of AD is correct. Notably, the current treatment regimen, including application, should be reviewed with both the patient and the family to ensure optimal use and adherence.[35,44]

When to consider treatment failure. There is no specific time after initiation to demonstrate the efficacy of TCSs, given the range of potency and dosage forms. The SC recommends using TCSs for up to 4 weeks for active treatment and 2 to 3 times weekly for preventative treatment. Studies have shown that acute treatment with potent TCSs reduces disease burden in as early as 3 days, with continual improvement over 3 weeks for moderate-to-severe AD.[49,64] However, the SC acknowledges that the need for consecutive daily TCS use for more than 4 weeks may not be a reasonable definition of treatment failure in many patients with AD, particularly those with severe disease who may need to apply TCSs daily to different lesions as long as necessary to maintain disease control.

Role of current and emerging systemic therapies in the management of moderate-to-severe AD

Until recently, the only FDA-approved systemic treatment for moderate-to-severe AD was corticosteroids, owing to their broad label for inflammatory skin disease. Patients are either treated off-label with immunosuppressants, which are associated with significant side effects, or more commonly, receive no systemic treatment. There is, therefore, a need for safe, approved, systemic therapies for patients with moderate-to-severe AD. The SC evaluated and provided recommendations for several of the systemic treatments currently in use for moderate-to-severe AD and for dupilumab (Table VI). Dupilumab was recently approved by the FDA for the treatment of moderate-to-severe AD in adults but was an investigational agent at the time of SC meetings.

Recommendations for current systemic treatments. Phototherapy is recommended by the AAD as a second-line treatment after topical therapy. Several forms of ultraviolet (UV) light therapy have been shown to be beneficial for disease and symptom control, including natural sunlight, narrowband UV light B, broadband UV light B, UV light A1, topical and systemic psoralen plus UV light A, ultraviolet A and B light, and Goeckerman therapy.[11] However, there are no comparative trials between these forms of light. The SC recommends narrowband UV light B because of its low-risk profile, relative efficacy, availability, and provider comfort level.[11] Although several trials have demonstrated the efficacy of phototherapy in patients with AD,[65-68] this may not be available or practical for many patients.

Systemic steroids are approved by the FDA for patients with moderate-to-severe AD, owing to their broad label for inflammatory skin disease in both adult and pediatric populations; however, there are minimal safety and efficacy data for their use in AD and they are not recommended by the AAD. Although the Atopic Dermatitis Practice Parameter recognizes widespread use of systemic steroids, it points to paucity of controlled studies in AD.[44] In the few placebo-controlled studies conducted in pediatric patients, systemic steroids significantly improved AD symptoms without significant side effects.[69-71] However, these

TABLE VI. Recommendations for role of systemic therapies in adults with moderate-to-severe AD

Recommendation	Voting results	
	Strength of recommendation*	Level of consensus†
Role of nonbiologic systemic therapies (N = 11)‡	7.5	80
1. Many patients with moderate-to-severe AD are not receiving systemic therapy because of lack of approved, safe, and effective therapies and significant burden of adverse events with off-label use of currently available immunosuppressants.		
2. Phototherapy, especially NB-UVB, can be used as a treatment for moderate AD and as maintenance therapy for patients with chronic disease. There are no well-conducted studies investigating the time to assessment of nonresponse for phototherapy of AD. Phototherapy is often administered 2-3 times per week and is discontinued if no improvement is seen in 4-8 wk. Phototherapy may not be accessible or practical for many patients.		
3. Systemic steroids are effective, but are associated with unacceptable short- and long-term adverse events and, therefore, should be used with caution only for severe exacerbations for short courses (no more than 2 wk). Adverse events associated with systemic steroids include hypertension, glucose intolerance, gastritis, weight gain, decreased bone density, adrenal suppression, and emotional lability. Rebound flares almost always occur after stopping treatment. Repeated courses of oral or injectable steroids are not recommended.		
4. There are few studies in the literature comparing various systemic immunosuppressive treatments, none of which are FDA-approved for moderate-to-severe AD.		
− Because of safety concerns, cyclosporine is not recommended for longer than 1 y. While on treatment, patients should be monitored for potential adverse effects, which often limit treatment duration. These include nephrotoxicity, hypertension, infection, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma. At optimal dosing, disease improvement should be seen within 4 wk of treatment with cyclosporine A, but response may be seen as early as 1-2 wk.		
− The time to maximum effect of methotrexate averages 10 wk, with minimal to no further efficacy after 12-16 wk, even with further dose escalation. Severe adverse effects, including bone marrow suppression, pulmonary fibrosis, risk for skin cancer, and lymphoma, have been reported while on methotrexate.		
− Studies have demonstrated a delayed time to response with azathioprine therapy in the treatment of AD. Some patients demonstrate delayed improvement only after 12 wk of treatment. Nausea, vomiting, and other gastrointestinal symptoms (eg, bloating, anorexia, and cramping) are common while on azathioprine. In some patients, azathioprine use has been associated with an increased risk of bone marrow suppression, infection, lymphoma, and nonmelanoma skin cancer development. Because of the delayed onset of improvement in AD, azathioprine is not commonly used.		
− Insufficient data exist to make recommendations regarding the optimal mycophenolate mofetil dosing or duration of therapy. Clinical improvement with mycophenolate mofetil is delayed, with initial response varying from 3 to 10 wk after treatment is initiated. Bone marrow suppression, infection, and lymphoma have been associated with mycophenolate mofetil.		
5. Omalizumab is not approved by the FDA and has not been shown to provide clinical efficacy in the treatment of AD.		
6. Although allergen-specific immunotherapy has not demonstrated consistent clinical efficacy in the treatment of AD, subcutaneous immunotherapy might be considered in selected patients with AD and aeroallergen sensitivity.		
Role of emerging biologics (N = 11)‡	9	82
1. Dupilumab has shown strong efficacy and safety for treatment of moderate-to-severe AD in adults. Considering the safety profiles of conventional systemic therapies, which are not FDA-approved for AD treatment, it is recommended that dupilumab be used as a first-line systemic treatment in adults with moderate-to-severe AD who are uncontrolled with topical therapies.		
2. If future biologics or small molecules become available for AD, their safety and efficacy data will have to be evaluated to determine their placement in therapy.		

NB-UVB, Narrowband ultraviolet B.

*Median score on a 1-9 scale.

†Percentage of votes with a score of 7-9 on a 9-point scale.

‡Number of the 11 SC members who voted. The patient advocate representative voted only on those questions for which she felt qualified to contribute from a patient perspective.

studies had few patients (<30) and the treatment time was short (3 days to 8 weeks). Furthermore, a study comparing cyclosporine A with oral prednisolone in adults was stopped because of severe side effects in the steroid arm.[72] The SC does not recommend the use of systemic steroids in most situations because they are poorly tolerated and often lead to disease exacerbation upon treatment discontinuation. Systemic steroids may be used with caution only for short courses in patients with self-limited, severe exacerbations while maximizing topical therapy or as a bridge to another nonsteroid systemic therapy.

TABLE VII. Summary of select investigational and recently approved agents for AD

Name	Company	Target	Phase
Small molecules			
Apremilast[80,81]	Celgene	PDE4	2
Baricitinib[82]	Eli Lilly	JAK	2
Crisaborole[83]	Pfizer	PDE4	FDA-approved for mild-to-moderate AD in patients older than 2 y
DS107[84,85]	DS Biopharma	Unknown*	2
Fevipiprant[86]	Novartis	Prostaglandin D_2 receptor 2 (CRTh2)	2
Timapiprant (OC000459)[87]	Atopix Therapeutics	Prostaglandin D_2 receptor 2 (CRTh2)	2
Tofacitinib[88]	Pfizer	JAK	2
Biologics			
BMS-981164[89]	BMS	IL-31	1
Dupilumab[90]	Sanofi-Genzyme and Regeneron	IL-4 and IL-13	FDA-approved for moderate-to-severe AD in adults
Fezakinumab (ILV-094)[91]	Pfizer	IL-22	2
Lebrikizumab[92,93]	Roche	IL-13	2
Nemolizumab (CIM331)[94]	Galderma R&D	IL-31	2
Tralokinumab[95,96]	LEO Pharma/AstraZeneca	IL-13	3

JAK, Janus kinase; *PDE4*, phosphodiesterase 4.
*Contains active biolipid dihomo-γ-linolenic acid, a component of healthy skin.

According to the AAD guidelines, the most commonly used systemic steroids for patients with AD are prednisone and prednisolone, which are both available as tablets or oral solution, and triamcinolone acetonide, which is available as an intramuscular injection. Dosing is based on body weight, and most providers use a dosage range of 0.5 to 1.0 mg/kg. Tapering is recommended to decrease the risk of adrenal suppression. Regardless of the tapering schedule, flares may be expected upon discontinuing steroid use.[11]

Several other immunosuppressants are used off-label for the treatment of moderate-to-severe AD, including cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, omalizumab, and allergen-specific immunotherapy, but there are few head-to-head studies comparing their efficacy in AD. Of these agents, the SC considers cyclosporine the most effective. In adult patients, cyclosporine A was superior to prednisolone and UV light A and B in head-to-head clinical trials, while offering similar efficacy to enteric-coated mycophenolate sodium, and was superior to intravenous immunoglobulin in a small pediatric study.[73] Cyclosporine A is associated with mean clinical improvement of 53% to 95% in AD severity after short-term treatment of 10 days to 8 weeks.[37] Despite its efficacy, significant safety concerns (including nephrotoxicity, hypertension, and infection) often limit treatment duration. Extensive monitoring, including blood pressure, renal function, lipids, and liver function, is recommended and treatment duration should not exceed 1 year.[11]

SC recommendations and considerations for other immunosuppressants are presented in Table VI. For more specific information regarding dosing and other treatment considerations, the SC refers the readers to the appropriate treatment guidelines.

Although the American Academy of Allergy, Asthma, and Immunology Practice Parameters for AD and immunotherapy include allergen-specific immunotherapy for patients with AD with aeroallergen sensitivity,[44,74] a recent systematic review was not able to find strong evidence to support its use.[75] In some patients, allergen-specific immunotherapy may exacerbate AD.[40,76] Aeroallergens are a trigger for exacerbations in adult AD, and pruritus and skin lesions can develop after challenge with aeroallergens.[36] Therefore, the SC recommends that subcutaneous immunotherapy be considered in select patients with AD with documented environmental allergies. Patients should be closely monitored and treatment discontinued if symptoms worsen.

Finally, although there are some data on the use of intravenous immunoglobulin therapy in patients with severe AD, recommendations on its use cannot be made at this time given the limited data. The SC refers readers to the appropriate guidelines for more information on intravenous immunoglobulin.

Emerging targeted therapies for AD. Several targeted therapies, both small molecules and biologics, are under investigation for the treatment of moderate-to-severe AD. Some of these therapies, such as apremilast, are approved for other inflammatory disorders. In a phase 2 study of adults with moderate-to-severe AD, apremilast, an oral phosphodiesterase 4 inhibitor, led to no significant improvement.[77] Crisaborole ointment 2%, also a phosphodiesterase 4 inhibitor, reduced AD severity compared with vehicle in 2 phase 3 trials in children and adults with mild or moderate AD after 28 days of treatment and was approved by the FDA in December 2016 for use in mild-to-moderate AD in patients 2 years or older.[78] Two other small molecules, ODC-9101 and fevipiprant, which target the chemoattractant receptor-homologous molecule expressed on T_H2 cells, are in phase 2 trials for adults with moderate-to-severe AD. mAbs that target either cytokines or their receptors to block AD-related immune pathways are also in development.[79] A list of several investigational and recently

TABLE VIII. Recommendations on shared decision making in the treatment of AD

Recommendation	Voting results	
	Strength of recommendation*	Level of consensus†
Shared decision making (N = 11)‡	9	100
1. The treatment of AD should be based on shared decision making between the patient and the provider.		
2. This includes a discussion between the patient and the provider regarding the following:		
– Treatment goals and expectations		
– Strategy planned to reach these goals		
– Therapeutic options		
– Risks and benefits		
– Comorbidities		
– Patient preference		
– Socioeconomic considerations		
3. Patient and health care provider education programs are an important element of shared decision making.		

*Median score on a 1-9 scale.
†Percentage of votes with a score of 7-9 on a 9-point scale.
‡Number of the 11 SC members who voted. The patient advocate representative voted only on those questions for which she felt qualified to contribute from a patient perspective.

TABLE IX. Highlights

- Several lines of evidence indicate that AD is a systemic disease, suggesting that systemic treatment may be an important strategy for disease control.
- Moderate-to-severe AD may be considered when there is a minimum involvement of 10% BSA or if a patient has individual lesions with moderate-to-severe features, involvement of highly visible areas or areas important for function, or has a significantly impaired QOL.
- Treatment failure may be defined as inadequate clinical improvement, failure to achieve stable long-term disease control, presence of ongoing impairment while on treatment, or unacceptable adverse events. There is no generalizable time to treatment failure for topical treatments. If failure is suspected, patient adherence should be assessed.
- Given the lack of safe and approved treatments for adults with moderate-to-severe AD, the SC recommends dupilumab as a first-line systemic treatment option for adults with moderate-to-severe AD whose disease is not controlled by topical treatment.
- When choosing a therapy for patients with moderate-to-severe AD, it is important to include the patient in the decision-making process.

approved agents for moderate-to-severe AD is provided in Table VII.[80-96]

Dupilumab, an mAb that targets the shared α subunit of the IL-4 and IL-13 receptors and effectively blocks T_H2 immune response, was recently approved for the treatment of moderate-to-severe AD in adults 18 years or older whose disease is not adequately controlled with topical treatments.[90] In 2 independent, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials in adults with moderate-to-severe AD, patients received dupilumab 600 mg subcutaneous injection at week 0 followed by dupilumab 300 mg every other week. Patients treated with dupilumab had significantly greater improvement in Investigator's Global Assessment score than those receiving placebo after 16 weeks of treatment. Results from both dupilumab groups in the 2 trials were significantly better than placebo in other measures, including EASI-50, EASI-90, BSA affected, Scoring Atopic Dermatitis, Global Individual Signs Score, and pruritus scores ($P < .001$ for all comparisons). Dupilumab was well tolerated in these trials, with only headache, nasopharyngitis, conjunctivitis, and injection-site reactions being encountered significantly more often than in the placebo-treated patients.[97] In a third phase 3 trial of the same dupilumab dosing regimen in combination with TCSs in adults with moderate-to-severe AD, the safety profile of dupilumab plus TCSs at week 52 was similar to that at week 16. Discontinuations due to adverse events were similar between the monotherapy trials at week 16 (1.9%) and the combination trial at week 52 (1.8%).[90] Despite these favorable safety results, it should be stressed that the long-term safety profile of dupilumab monotherapy is unknown. Given the strong evidence for the efficacy and safety of dupilumab in adults with moderate-to-severe AD and the significant safety concerns associated with conventional systemic therapies, the SC recommends dupilumab for first-line systemic treatment in adults with chronic moderate-to-severe AD who are uncontrolled with topical therapies.

A phase 2 study of dupilumab in pediatric patients (age ≥6 to <18 years) was recently completed; however, results are not yet available.[98] Recommendations for the use of dupilumab in pediatric patients will depend on the safety and efficacy results in this population in phase 3 studies.

Other agents in development for adults with moderate-to-severe AD include lebrikizumab and tralokinumab, which target IL-13, and 2 agents that target IL-31, nemolizumab and BMS-981164 (Table VII).[79] If these or other agents become available for AD, their role will have to be evaluated on the basis of their efficacy and safety profile.

Shared decision making

The treatment of AD must be based on a shared decision between the patient and the provider (Table VIII). Patient preferences and goals should be considered key factors when selecting a treatment regimen. The SC recommends that patients be appropriately informed about treatment goals and expectations, limitations, and the strategy planned to reach these goals. Providers should give patients a realistic overview of the risks and benefits of a given therapy, taking into account comorbidities, which may affect treatment choice. Finally, because systemic treatments are often prescribed off-label, providers should also discuss with patients the likelihood of reimbursement.

The SC also stresses the importance of access to structured patient education programs and shared decision-making resources. Patients should be provided education on all available therapies, including oral agents, injectables, and topical agents, before choosing a therapy. Patients should be informed of the therapeutic options and reasons for recommending a particular therapeutic approach so that they can be an active participant in selecting a treatment. In randomized controlled trials, therapeutic patient education significantly improved AD severity and QOL in both children with AD and adults with moderate-to-severe AD.[99]

DISCUSSION

To address current unmet needs in AD, a multidisciplinary SC, consisting of dermatologists, allergists, and a patient advocacy group representative, convened from July 2016 to January 2017. The SC identified and prioritized a number of essential questions concerning the evaluation and management of AD in the era of biologic therapies and crafted recommendations on the basis of a review of the literature and expert opinion. These expert recommendations are intended to provide practical, clinical guidance to both dermatologists and allergists treating moderate-to-severe AD (Table IX).

The recommendations highlight several key areas in moderate-to-severe AD for which standardized guidance and robust, validated tools are still needed. Although there are many tools and scales for AD diagnosis and grading, current tools are more amenable to clinical trials and population-based studies. The SC acknowledges a need for simple diagnostic criteria for AD suitable for use in daily practice that not only consider the objective measures of disease severity, but also incorporate QOL measures. In addition, there is a lack of guidance and objective criteria for determining treatment failure and response to treatment. None of the biomarkers under investigation for monitoring treatment response or disease severity has sufficient evidence to be used in a clinical setting. The SC recommended 4 types of treatment failure in patients being treated for AD; however, it is difficult to generalize the time to treatment failure, given the range of potency and dosage forms of steroids and the variable severity of disease.

The treatment options for patients with moderate-to-severe AD who do not respond to topical treatments have been suboptimal. The SC agreed with current guidelines, which do not recommend the use of systemic corticosteroids given both short- and long-term side effects. Although other systemic immunosuppressants may be effective, they have significant safety concerns. In addition, the lack of robust clinical data and head-to-head trials makes it difficult to assess their comparative efficacy. The SC strongly recommends that providers include patients in treatment decisions. This shared decision making is key to maximizing patient adherence and treatment success.

On the basis of clinical data to date and the lack of suitable options for patients with moderate-to-severe AD, the SC recommends dupilumab as a first-line systemic treatment option in adults. Dupilumab was recently approved by the FDA for moderate-to-severe AD in adults whose disease is not controlled by topical treatments. In 2 phase 3 clinical trials, dupilumab significantly improved AD symptoms compared with placebo with a tolerable safety profile, though the long-term safety is unknown. As other targeted agents are investigated for moderate-to-severe AD, their safety and efficacy will have to be evaluated to understand the role that they might play in the AD treatment paradigm.

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