Atopic Dermatitis Needs Assessment

Atopic dermatitis (AD) affects more than 4% of adults and 10% of children, making it the most common chronic inflammatory skin disease.[1,2] A recent longitudinal study found that childhood AD symptoms persisted well into adolescence and longer, suggesting that AD may persist more commonly than previously recognized.[3] Furthermore, AD poses a significant economic concern and a substantial burden on physical and emotional health and social wellbeing.[4]

Treatment failure is an unfortunate issue surrounding AD. One reason for treatment failure is that AD has a highly complex clinical presentation, leading to frequent misdiagnosis.[5] One study found that more than one-half of patients referred to a specialist were not administered treatment.[6] Clinicians often do not have the time for proper education of patients and caregivers surrounding treatment, which can lead to compliance issues.[7] However, the past year has shown enormous progress when it comes to approved therapies.

In a recent editorial, Jonathan and Nanette Silverberg stated, "AD has just begun to command the respect it deserves as a chronic disease with negative life impact and comorbidities. The future holds new definitions, better recognition of disease manifestations, superior surveillance for comorbidities, and an impressive improvement in therapeutic interventions. This is truly an exciting time for patients with AD, the people who suffer with them, and clinicians who treat AD." Therefore, educating clinicians on diagnostic criteria, current treatment guidelines, and new and emerging therapies will reduce treatment failure rate.

In this period of rapid pharmaceutical progress in AD, up to date education is critical for dermatologists, allergists, and all primary care physicians providing care to atopic dermatitis patients.

This comprehensive needs assessment is based on gap analysis of the practices and educational needs of primary care providers, allergists and dermatologists who may encounter patients with AD. This document includes a review of the recent medical literature, current practice guidelines, and relevant accredited medical education activities. Through this assessment, National Jewish Health has determined that an educational activity is warranted.

Gap Analysis 1

Clinicians need the knowledge and skills to properly evaluate and diagnose patients with AD

Knowledge/practice gap	Clinicians are challenged to properly assess and diagnose patients with AD.
Desired results	Clinicians are equipped with the knowledge and tools to properly assess and diagnose patients with AD.
Learning objective	1-Describe the burden of illness in patients with AD using different assessment tools 2-Identify patient centered assessment measures 3-Identify barriers to the proper diagnosis of patients with AD 4-Assess the clinical phenotype of AD

AD (eczema) has a detrimental effect on the lives of patients and their families, including impact on quality of life (QoL) as well as social, economic, academic, and occupational consequences.[4] Not surprisingly, many studies have observed that QoL decreases as AD severity increases.[8-10] In children, effects on physical health (itching, scratching, sleep, pain), emotional health (irritability, crying), and social functioning are profound. One study examining children with chronic diseases found that generalized AD had the second-largest impact on QoL.[11] Adult patients appear to be most affected by physical symptoms (itch and sleep disturbance) and emotional impact, and sleep and emotional burdens are also seen in parent caregivers of young children with AD.

The annual costs of AD in the United States are thought to exceed $5.3 billion.[4] The International Study on Life with Atopic Eczema reported that 32% of participants believed that AD affected their school or work life, and 14% of adults believed that AD had hindered their career progression.[12]

The wide-ranging impact of AD on patients and their families dictates a need for clinician education about the burden of disease and quality of life measures in AD .

The clinical phenotype of AD is highly complex, varying substantially based on patient age, disease severity, age of onset, and ethnic origin of the patient.[13] At least four distinct clinical features have been defined, which include infantile, childhood, adolescent/adult, and elderly phenotypes. AD presents as very mild to extremely severe phenotypes.

The onset of AD may occur at various life stages; from very early (between 3 months and 2 years), early (between 2 and 6 years), childhood (between 6 and 14 years), adolescent (between 14 and 18 years), adult (between 20 and 60 years), to very late (older than 60 years).[13]

The diagnosis of AD is based on historical features, skin morphology and distribution of lesions and associated clinical features. There are no reliable biomarker or serological tests that can support the AD diagnosis.

Numerous instruments for the assessment of AD severity have been developed, -as many as 28 scales-, the most commonly used being the Scoring Atopic Dermatitis (SCORAD) Index, the Eczema Area and Severity Index (EASI), the Investigator Global Assessment (IGA) tools and the Six Area, Six Sign Atopic Dermatitis (SASSAD) tools. These tools are well validated by the literature and measure objective disease features and extent, intensity and history of eczema, as well as subjective features such as pruritus and sleep loss.[14]

Additional scales that assess patients' quality of life, such as the Dermatology Life Quality Index (DLQI)Children's Dermatology Life Quality Index (CDLQI), the Dermatitis Family Impact (DFI) have also been developed. Patients with atopic dermatitis frequently report lack of sleep due to pruritus and itching, pain related to sore and itchy skin, negative interference on school, work, interpersonal relationships and normal activities and most importantly; depression and anxiety. [14]

These scales were primarily designed for use in clinical trials and are not applicable in clinical practice. Therefore, none of them have been recommended as the golden standard.[14]

The irregular use of different assessment scales among physicians in clinical practice results in high variability in reported outcomes. An international effort was undertaken to standardize measured outcomes by looking at signs and symptoms of AD. To this end, the Harmonizing Outcome measure for Eczema (HOME) initiative study, has defined a core outcome set (COS) across the main outcome domains of clinical signs, symptoms, quality of life and long-term control as mandatory measures in all atopic eczema trials to ensure cross-trial comparison.[15]

A study assessing the intra and inter reliability of the SCORAD, EASI and IGA tools showed no significant advantage of one method over the other, and recommended the use of at least 2 independent measurements simultaneously to ensure reliability.[16]

Each tool has different features that may allow a patient centered approach to diagnosis. For example, EASI uses objective physician estimates of disease extent and severity while SCORAD incorporates objective and subjective patient perceptions of sleep loss and itch[4]. In contrast, the Patient Oriented Eczema Measures (POEM) tool is a unique approach that measures severity from a patient perspective with seven questions relating to symptoms and their frequency. The HOME initiative encouraged all physicians to use POEM as the core outcome instrument to measure symptoms of AD in all future trials[3,4].

To minimize variability in measurements of AD severity, clinicians should be educated about all the assessment tools available and use a patient centered diagnostic approach.

Furthermore, several studies confirmed variations of the clinical phenotype depending on ethnic origin of the patient. For example, one study reported a different clinical picture of AD lesions in African American patients compared to the Caucasian patient population.[17] Such broad clinical presentation leads to a frequent misdiagnosis of AD [5] and to its differential diagnosis.

The diagnosis of AD may be straightforward in infants and children but can be difficult to make in adults. The differential diagnosis of adults and children with AD includes seborrheic dermatitis, psoriasis, allergic contact dermatitis, molluscum dermatitis, tinea corporis, mycosis fungoides, dermatomyositis, pityriasis lichenoides chronica, Langerhans cell histiocytosis, polymorphous light eruption, actinic prurigo, and nutritional deficiency.[5]

Clinicians need to recognize the various AD clinical phenotypes in both adults and children to provide the correct diagnosis of AD.

Gap Analysis 2

Clinicians must be educated on the latest treatment guidelines and expert recommendations

Knowledge/practice gap	Lack of knowledge among practitioners of the latest treatment guidelines and expert recommendations in the management of AD.
Desired results	Physicians are confident in treating patients using the latest treatment guidelines and expert recommendations in the management of AD.
Learning objective	Manage patients with AD in accordance with the latest treatment guidelines and expert recommendations

Clinicians must be knowledgeable about the treatment guidelines of AD, and expert recommendations in order to improve patient outcomes. Recent guidelines include those published by the American Academy of Dermatology in 2014 and by the American Academy of Allergy, Asthma & Immunology in 2012.[18-22] In addition, the American Academy of Dermatology published recommendations from an expert panel of the International Eczema Council for patient advancement to systemic therapy in severe cases of AD. All dermatologists, allergists and primary care physicians need to be educated on the current treatment guidelines to provide the best possible treatment to patients with AD.

The standard pharmacotherapy of AD remains an area of controversy, and clinicians' concerns of side effects have led to under prescribing of validated treatments of AD.

When AD cannot be controlled with moisturizers alone, topical corticosteroids are first line therapy.[18] For instance, a study of AD in children showed that less than one third of all patients, and less than one quarter of patients younger than 2 years were treated with topical corticosteroids.[23] In addition, even when topical corticosteroids are prescribed, poor communication between clinicians and patients and particularly a lack of patient education have resulted in compliance issues.[24]

The topical calcineurin inhibitors (TCIs) pimecrolimus and tacrolimus are FDA-approved as second-line therapies for AD patients greater than 2 years of age. In 2006, a Boxed Warning was issued for TCIs about rare cases of lymphoma with long-term use.[25] Even after the American Academy of Dermatology the American College of Allergy, Asthma and Immunology, and the American Academy of Asthma, Allergy and Immunology issued statements confirming the safety of TCIs and expressed concerns about the Black box warning, the prescribing of the TCIs to eligible patients remained less than optimal.

Similarly, occlusive wet wrap therapy (WWT) is effective in reducing severe disease and is recommended in managing flares and resistant AD. This treatment is however underused in practice due to the lack of patient education and clinician training, and exaggerated concerns of increased systemic absorption side effects.[26]

The multidisciplinary healthcare team member must be thoroughly educated about treatment guidelines at all severity levels of the disease to provide integrated care to AD patients.

The guidelines also emphasize the importance of patient education in the management of AD. Yet patients and caregivers commonly fail to apply prescribed treatment regimens in practice, which reinforces the need for clinician education.

The use of unproven treatments such as homeopathic and herbal remedies is seen in 42.5% of caregivers of children with AD, and 24% report non-adherence with prescribed regimens.[27] In developing countries, steroid phobia leads to under treatment and proves more dangerous than the overuse of topical corticosteroids in the management of AD.[8] In contrast, one study reported an 89% reduction in symptom severity following repeated education and demonstration of topical therapies, proving the positive impact that patient education can have on clinical outcomes.[28] The Eczema Action Plan (EAP) was recently proposed to help patients and providers in managing their eczema.[29] Written action plans have added value in other chronic diseases like asthma, and a growing body of literature supports the use of a similar plan for AD.[30,31]

In depth education about current treatment guidelines and expert recommendations, including pharmacotherapy and patient education is necessary among specialists and primary care providers, and will lead to improved prescribing practices.

Gap Analysis 3

Clinicians must be familiar with the latest advances in therapy and incorporate new drugs to the treatment of AD

Knowledge/practice gap	Clinicians are uncertain about the role of new therapies in the treatment and management of AD and may be unware about data on investigational agents. The usual time lag before recently approved agents are incorporated to guidelines causes uncertainty and lack of consensus among practitioners about best prescribing practices for these drugs.
Desired results	Clinicians are prepared to include new therapies in the treatment and management of AD and are aware of the latest data on emerging agents.
Learning objective	1-Apply knowledge of the pathophysiology of AD to the selection of treatment options 2-Summarize research on the safety, efficacy, and mechanisms of action of emerging therapies for the treatment of AD 3-Incorporate latest FDA approved drugs to the treatment plan following safety and efficacy results from clinical trials

Due to the increased understanding of the pathogenesis of AD in the past decade, there have been exciting and profound advances in treatment, particularly within the past year. In a recent editorial, Jonathan and Nanette Silverberg stated, "One of the most promising new developments in our understanding of AD is the recognition that AD is an immune-mediated disorder largely driven by T-helper 2 cytokines, interleukin-4, and/or interleukin-13." They added, "These insights have directly translated into the development of novel biologic agents targeting these cytokine pathways. The first such biologic agent to be approved by the FDA for AD was dupilumab, with multiple other biologic, systemic, and topical agents in the pipeline for AD."[32]

<u>Topical phosphodiesterase-4 (PDE4) inhibitors</u>

Intracellular cAMP is thought to decrease the production of inflammatory mediators. The inhibition of PDE4 increases cAMP which impacts intracellular inflammation. By altering the levels of PDEs and inhibiting intracellular inflammation, PDE-4 inhibitors are especially valuable in fighting itch and pruritus, and may provide an alternative to topical corticosteroids and calcineurin inhibitors.

Crisaborole, a non-steroidal topical PDE4 inhibitor, was recently approved by the FDA in December 2016 for the treatment of mild to moderate AD in patients 2 years or older. The approval was based on two clinical trials that randomized subjects to receive either crisaborole or a vehicle twice daily for 28 days.[33] The primary endpoint was success in ISGA score on day 29. Success was defined as the proportion of patients achieving an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. Subjects receiving crisaborole had significantly ($p<0.001$) greater ISGA success compared to vehicle controls.[33] Crisaborole is particularly beneficial in itching and pruritus and subsequently improves quality of life in affected patients. Crisaborole is the first in its class topical PDE4 inhibitor approved for treatment of AD since the introduction of the TCIs in 2002. Crisaborole is applied twice a day and may provide an alternative to topical steroids or TCIs.

Apremilast is an oral PDE4 inhibitor that is already approved by the US Food and Drug Administration for psoriasis and psoriatic arthritis, and is under investigation for the treatment of AD. Phase 2 trials have been completed. A small study examining apremilast treatment of 30 mg twice daily showed symptom improvement, with most patients showing a >75% improvement based on the ISGA.[34]

T-helper 2 cell (Th2) antagonists

Acute and subacute AD lesions have shown increased levels of T-helper type 2 (Th2) cells. Increased skin expression of interleukin (IL) -13 and IL-4 (Th2 cytokines) was present in acute AD while skin lesions of chronic AD patients showed an increase in IL-5 (Th2 cytokine), IL-12 and interferon (IFN)- γ (Th1 cytokines), and a greater eosinophil infiltration.[35] IL-4 induces the differentiation of Th2 cytokines and IL-13 attracts Th2 to AD lesions. IL-13 is also thought to indirectly facilitate IL-5 expression and promote eosinophil infiltration to AD lesions.

Dupilumab was approved by the FDA in March 2017 for the treatment of moderate to severe AD. It is a fully human monoclonal antibody directed against the IL-4 receptor α (IL-4Rα) subunit that blocks the signaling of IL-4 and IL-13. Dupilumab showed superior efficacy in monotherapy in two phase 3 clinical trials (SOLO1 and SOLO2) of adults with moderate to severe AD, and in the CHRONOS study when used in combination with corticosteroids. Dupilumab significantly ($p<0.001$) improved clinical severity, pruritus, and patient-reported symptoms such as sleep disturbance, anxiety and depression, and QoL compared to placebo.[36] Furthermore, the CHRONOS study showed significantly ($p<0.0001$) greater improvements in measures of overall disease severity at 16 weeks and 52 weeks when dupilumab was added to standard topical corticosteroid treatment compared to steroid treatment alone. All 3 studies showed an increased rate of conjunctivitis, yet this side effect was not observed in previous studies of dupilumab for asthma and sinusitis. [37] Dupilumab is the first biologic approved for the treatment of moderate to severe AD and is now recommended as first line therapy for this indication.

Lebrikizumab is an IL-13 inhibitor that has completed phase 2 trials. It was studied in the TREBLE study, a phase 2 randomized placebo-controlled trial of adult patients with moderate to severe AD who had inadequate response to corticosteroids at one year. Patients continued steroid topical therapy while on Lebrikzumab 125mg. Significant improvements were seen in EASI50 and SCORAD50 response rates in patients taking Lebrikzumab 125mg every 4 weeks.[38]

Tralokinumab, another IL-13 monoclonal antibody was tested in a dose-ranging phase 2b study of patients with moderate to severe AD. The high dose of tralokinumab significantly reduced symptom severity and improved QoL and itching on the EASI scale, when compared to placebo. Tralokinumab in monotherapy is now being tested in the phase 3 ECZTRA1trial.[39]

Nemolizumab is a monoclonal antibody directed at IL-31R. IL-31R is implicated in the pathogenesis of itch. A phase 2 trial investigating Nemolizumab in a dose-ranging manner in patients with moderate to severe AD showed significant symptom improvement in the scores of pruritus ($p<0.01$) using the Visual Analog Scale (VAS). Pruritus severity declined by 63.1% with the highest dose of 2.0 mg/kg. However, the group given the middle dose of 0.5 mg/kg showed the greatest treatment benefit and the best benefit-to-risk profile.[40]

Janus kinase (JAK) inhibitors

The Janus Kinase pathway is associated with inflammatory and autoimmune diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Inflammatory cytokines use the JAK pathway to stimulate intracellular signaling. Furthermore, JAK inhibitors have been successful in the treatment of rheumatoid diseases further proving their inflammatory role.[41]

Upadacitinib, tofacitinib and **baracitinib** are JAK inhibitors that have been tested in phase 2 clinical trials and are currently under further investigation for AD.[42]

Other agents in the pipeline with different mechanisms of action:

Ustekinumab is a human monoclonal antibody targeting the p40 subunit of IL-12/23 that effectively suppresses the IL-23/Th17 pathway.[43] The drug is FDA approved for moderate-to-severe psoriasis, and phase 2 trials are currently underway for AD. A case study reported patient clearance at week 19 after four doses of 45 mg ustekinumab.[44]

Tradipitant, -a neurokinin-1 receptor antagonist-, has completed phase 2 trials for the treatment of chronic and treatment resistant pruritus of AD in adults, and showed improvement in the Worst Itch VAS scale and disease severity. The itch sensation is thought to be induced in part through the binding of substance P to neurokinin-1 receptors.[45,46]

Educating clinicians on the pathophysiology of the disease in relation to targeted AD treatments will result in patient centered prescribing. Moreover, programs that highlight the safety, efficacy and mechanisms of action of new and emerging treatments of AD, especially those agents that have not yet been included in evidence based guidelines will assist physicians in making well informed prescribing decisions.

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