The Underrecognized Burden of Atopic Dermatitis in the United States

KEY TAKEAWAYS:

- Atopic dermatitis has a complex pathogenesis and heterogeneous presentation, and is associated with allergic, immune-mediated, and psychological comorbidities.
- Although it is often considered a childhood disease, atopic dermatitis affects approximately twice as many adults in the United States as it does children.
- Criteria exist for the diagnosis of the disease; however, they can be complex and not applicable to all age groups.
- Likewise, although biomarkers exist for the diagnosis of atopic dermatitis, many experts do not use them, citing their lack of reliability, validity, and availability.
- Once atopic dermatitis is diagnosed, clinicians can use one of several measures to assess disease severity. However, the complexity or novelty of some measures and the lack of objectivity, validation, or comprehensiveness of others make no single measure useful in every clinical practice.
- The management of atopic dermatitis requires a multifaceted approach to care. Given this, and in the absence of reliable diagnostic biomarkers and a single appropriate disease severity measure, management of atopic dermatitis among adult patients in the United States requires a treatment plan that considers both clinical outcomes and the patient’s quality of life.

INTRODUCTION: SCRATCHING THE SURFACE OF ATOPIC DERMATITIS

Atopic dermatitis, also called atopic eczema, is characterized by eczematous lesions with reddened, blistered, crusty, or oozing skin; lichenification (thickening); xerosis (dry skin); and pruritus (itching). It can occur on any area of the body, and its clinical presentation is highly varied. Although it is often considered a childhood disease, atopic dermatitis affects approximately twice as many adults in the United States as it does children. Atopic dermatitis places a substantial burden on patients and the health care system that includes increased hospitalizations and health care costs, as well as loss of work productivity and disability. Among patients with moderate or severe atopic dermatitis, for whom the disease is not adequately controlled on the standard of care, atopic dermatitis can decrease quality of life (QOL) dramatically. Multiple criteria are used in clinical trials to assess the severity of atopic dermatitis and the safety and efficacy of available treatments; however, no single tool is suitable for use in clinical practice. In the absence of reliable diagnostic biomarkers and a single appropriate disease severity measure, the management of atopic dermatitis among adult patients in the United States requires a treatment plan that considers both clinical outcomes and the patient’s QOL. This article will provide an overview of the disease course, pathogenesis, prevalence, burden, diagnostic criteria, and disease severity measures of atopic dermatitis, with a focus on management of more severe disease.

DISEASE COURSE, PATHOGENESIS, AND EPIDEMIOLOGY: IS ATOPIC DERMATITIS ONLY A CHILDHOOD DISEASE?

Atopic dermatitis has a heterogeneous disease course that may involve a relapsing-remitting presentation with episodic or acute flares, or chronic persistent disease. With flares, acute and subacute lesions are typically highly pruritic with erythematous papules and vesicles, excoriations, and serous exudate. Acute inflammation with exudation commonly appears in infantile
atopic dermatitis, with a presentation favoring the face and extensor regions.\(^3\) Chronic inflammation, which becomes more prevalent with age, often appears in flexural regions (eg, insides of the elbows and armpits).\(^2\)

The pathogenesis of atopic dermatitis is a complex interaction between epidermal barrier dysfunction, environmental and genetic contributions, and immune system activation.\(^1\) The strongest risk factor for atopic dermatitis is a family history of atopic diseases. Other well-established risk factors include living in an urban setting or dry climate, a lack of UV light exposure, a diet high in sugars and polyunsaturated fatty acids, high antibiotic usage prior to age 5 years, and diminished diversity of bacterial flora in the gut, among others.\(^1,6\) Symptom triggers include irritants such as smoke, pollution, dust, pollen, and detergents.\(^1\)

Atopic dermatitis is associated with allergic, immune-mediated, and psychosocial comorbidities. Individuals with a family history of asthma or allergic rhinitis are predisposed to the development of atopic dermatitis. Similarly, in some patients, the condition is preceded by the evolution of food allergies, asthma, and allergic rhinitis (ie, the “atopic march”).\(^2\)

As demonstrated in a cross-sectional study of data from the 2002 to 2012 National Inpatient Sample (N = 87,053,155; n = 19,486 patients admitted with atopic dermatitis), atopic dermatitis is associated with immune-mediated comorbidities affecting the skin (eg, erythema nodosum, systemic lupus erythematosus, scleroderma, vitiligo) and the endocrine (eg, Hashimoto disease, thyroiditis), gastrointestinal (eg, ulcerative colitis, celiac disease), hematologic (eg, granulomatosis with polyangiitis, pernicious anemia), and musculoskeletal systems (eg, multiple sclerosis, rheumatoid arthritis).\(^1\) The 2018 results of a cross-sectional study of data from the Atopic Dermatitis in America Survey showed that atopic dermatitis in adults (n = 602) was also associated with a higher prevalence of other comorbidities, including cardiovascular (eg, heart disease, high blood pressure) and psychological disorders or conditions (eg, depression, anxiety) (P < .0001 for all).\(^1\) Similar results were observed in a cross-sectional study of data from the 2013 US National Health and Wellness Survey (N = 71,182 subjects). Compared with matched controls without atopic dermatitis (n = 698), adult patients with atopic dermatitis (n = 349) were nearly 2 times more likely to report sleep disorders, depression, and anxiety (P < .001 for all).\(^2\)

Atopic dermatitis is recognized as one of the most common inflammatory skin disorders worldwide.\(^1\) The prevalence of atopic dermatitis peaks in early childhood, remains high throughout childhood, decreases in adolescence, and then remains stable throughout adulthood.\(^1\) Although it is often considered a childhood disease,\(^1\) atopic dermatitis affects approximately twice as many adults in the United States as it does children.\(^5,6\)

The results of a 2017 evaluation of data from the 2012 National Health Interview Survey estimated that atopic dermatitis or some sort of eczema affects 12% of children (range, 11.3%-12.7%) and 7.2% of adults (range, 6.9%-7.6%) in the United States.\(^1\) This suggests that approximately 9 million children and more than 18 million adults are likely to have atopic dermatitis in the United States (based on US Census Bureau estimates reporting 73 million children and 255 million adults in the United States in 2019).\(^1,6\)

### BURDEN OF DISEASE: EFFECTS ON PATIENTS AND THE HEALTH CARE SYSTEM

Atopic dermatitis can have a substantial impact on patients and the health care system. The progression of symptoms, such as pruritus and pain, can lead to increased hospitalizations and health care costs, as well as loss of work productivity and disability. The impact on patients’ QOL can be severe, with patients experiencing depression and sleep disorders, as well as avoiding social situations (Figure 1).\(^20-23\)

#### Economic Burden

A full exploration into the economic burden of atopic dermatitis in the United States is beyond the scope of this article; however, evidence suggests that health care resource utilization is higher among patients with atopic dermatitis.\(^24\) These patients have been shown to have a substantially greater annual number of emergency room visits, outpatient visits, and hospitalizations compared with patients with no atopic dermatitis.\(^25\) Costs associated with atopic dermatitis are approximately $7 billion a year (2020 US$), based on an estimated inflation rate of about 68%, as determined by the Consumer Price Index for Medical Costs. This includes $1.7 billion in direct costs, $1.04 billion in indirect costs, and $4.37 billion in intangible costs.\(^20,21\) (It is important to note that these numbers are based solely on the number of dollars, without regard to other influences, such as new treatments.)

#### Clinical Burden

The clinical burden of atopic dermatitis is high and can be illustrated in terms of disability-adjusted life-years (DALYs).\(^2,23\) One DALY equals 1 year of full health lost due to dying prematurely or to living with a related disability, on account of a disease.\(^1\) Results from the Global Burden of Disease Institute for Health Metrics and Evaluation determined that atopic dermatitis was associated with the highest age-standardized DALY rate among all skin diseases in 2017 (123 per 100,000 individuals; 95% uncertainty interval [UI], 66.8-205), with the next highest skin disease DALY rate being for psoriasis (70.0 per 100,000 individuals; 95% UI, 49.7-92.5).\(^3,4\)

#### Quality of Life

Among the greatest burdens of atopic dermatitis is its symptoms and their impact on patients’ QOL; these include pruritus, sleep disturbance, anxiety, depression, social embarrassment, interference with daily activities, and loss of productivity.\(^20,23\) QOL burden increases with disease severity and is particularly acute for patients with more severe disease.\(^2,19\)

In a cross-sectional burden-of-illness study of adult patients with atopic dermatitis (N = 1519) from clinical practices in the United States (the AD-AWARE study), patients with moderate or severe atopic dermatitis (n = 830) were found to be significantly more likely to report trouble sleeping (rating of 3.9 vs 1.1 on Patient-Oriented
Scoring Atopic Dermatitis [PO-SCORAD] visual analog scale), longer sleep latency (38.8 minutes vs 21.6 minutes), more frequent sleep disturbances (2.6 nights vs 0.4 nights, in the past week), and an increased need for OTC sleep medications (39% vs 21%) than those with mild atopic dermatitis ($P < .001$ for all). Additionally, approximately half (50.2%) of the patients with moderate or severe atopic dermatitis ($n = 417/830$), reported symptoms of anxiety or depression compared with 27.3% of those with mild disease ($n = 188/689$). Furthermore, approximately half (50.2%) of the patients with moderate or severe atopic dermatitis ($n = 417/830$), reported symptoms of anxiety or depression compared with 27.3% of those with mild disease ($n = 188/689$).17

Moreover, the results of a multinational, phase 2b, prospective study of patients with moderate to severe atopic dermatitis ($N = 380$), most of whom had recently used topical therapies, corroborated the heavy QOL burden for patients with more severe disease. 85.8% of a large subset ($n = 378$) of patients in this study experienced pruritus every day over a 2-week period; 60.5% of this subset reported the pruritus to be “unbearable” or “severe.”

**COMPLEXITY OF DIAGNOSIS**

The heterogeneous clinical presentation of atopic dermatitis, with its acute and chronic disease course, can affect appropriate diagnosis.1,2,13,35-37 Criteria exist for the diagnosis of atopic dermatitis; however, they can be complex and may not apply to all age groups.2,9 Although biomarkers exist for the diagnosis of atopic dermatitis, most International Eczema Council experts surveyed before the 2019 Society of Investigative Dermatology meeting did not use them, citing a lack of reliability, validity, and availability of these tests.10 Under these circumstances, atopic dermatitis is generally diagnosed based on clinical signs, historical features, morphology, and skin lesion distribution (Table 1).2,9

The 1980 Hanifin and Rajka criteria, one of the oldest and most well-known sets of diagnostic criteria established for atopic dermatitis, are comprehensive in nature and often used for clinical trials; however, the criteria can be impractical in clinical practice. Diagnosis requires the establishment of 3 of 4 major criteria and 3 of 23 minor criteria; some of the minor criteria are not well-defined or specific to atopic dermatitis or are very specific to atopic dermatitis and rare.7,24 The United Kingdom Working Party criteria were developed as a condensed version of the Hanifin and Rajka criteria, appropriate for epidemiologic and population-based studies; however, the original version is not applicable to very young children.7,9 The American Academy of Dermatology (AAD) established a streamlined version of the Hanifin and Rajka criteria that is appropriate for use in clinical practice and applies across all ages of affected patients.7

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*Because data were obtained via a self-administered internet-based questionnaire, real-world data from this study were limited due to self-reporting by patients and potentially different types of selection bias. For example, patients who participated in the study may have certain characteristics that differ from individuals who chose not to participate. In addition, the use of an internet-based survey may be representative of a particular population or perspective different from that supplied by other methods (eg, telephone interview). Furthermore, because patients were selected from academic medical centers, they may not reflect those found in community practice. Additional limitations were the cross-sectional study design and the subjective definition used for disease control.

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**Figure 1. Burden of Atopic Dermatitis in the United States**18-23
The International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes for atopic dermatitis (Figure 2) further complicate definitive diagnosis. Although these codes are more nuanced than those in the previous revision (ICD-9), they are likely to have poor predictive value of probable or definitive diagnosis of atopic dermatitis in the outpatient setting, as did the codes for atopic dermatitis in ICD-9. The International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes for atopic dermatitis include:

- L20.0 Besnier’s prurigo
- L20.8 Other AD
  - L20.81 Atopic neurodermatitis
  - L20.82 Flexural eczema
  - L20.83 Infantile [acute] (chronic) eczema
  - L20.84 Intrinsic (allergic) eczema
  - L20.89 Other atopic dermatitis
- L20.9 AD, unspecified

The SCORAD accounts for the extent and severity of signs of the disease (of dryness, lichenification, erythema, oozing/crusting, excoriation, and edema/papulation) and considers patient-reported outcomes (for sleep loss and pruritus). Adaptations of the SCORAD include the Patient-Oriented SCORAD (PO-SCORAD), which patients complete, and the objective SCORAD (oSCORAD), which excludes the patient-reported elements.

The US Food and Drug Administration (FDA) introduced the concept of a Physician Global Assessment in 1998; it has since recommended the use of a global assessment for primary end points in atopic dermatitis clinical trials. Many scales referred to by the terms "Investigator('s) Global Assessment" (IGA), "Physician('s) Global Assessment" (PGA), and "Physician('s) Global Evaluation" (PGE) have been used to assess atopic dermatitis severity in clinical trials. However, these scales differ widely, and this variety has

### Table 1. Diagnostic Features of Patients with Atopic Dermatitis

<table>
<thead>
<tr>
<th>Essential features (must be present)</th>
<th>Important features (seen in most cases, supporting diagnosis)</th>
<th>Associated features (nonspecific clinical associations to suggest diagnosis)</th>
<th>Exclusionary conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>Early age of onset</td>
<td>Atypical vascular responses</td>
<td>Scabies</td>
</tr>
<tr>
<td>Eczema (acute, subacute, chronic)</td>
<td>Personal and/or family history</td>
<td>Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis</td>
<td>Contact dermititis</td>
</tr>
<tr>
<td>Chronic or relapsing history</td>
<td>Atopy</td>
<td>Ocular/periorbital changes</td>
<td>Seborrheic dermatitis</td>
</tr>
<tr>
<td>Typical morphology and age-specific patterns (patterns include facial, neck, and extensor involvement in infants and children; current or previous flexural lesions in any age group; sparing of the groin and axillary regions)</td>
<td>Immunoglobulin E reactivity Xerosis</td>
<td>Ichthyosis</td>
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<td></td>
<td></td>
<td>Other regional findings (eg, periorbital changes)</td>
<td>Cutaneous T-cell lymphoma</td>
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<td></td>
<td></td>
<td>Perifollicular accentuation/lichenification/prurigo lesions</td>
<td>Psoriasis</td>
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### Select Severity Measures in Atopic Dermatitis

Some select measures of disease severity that are commonly used include body surface area (BSA) assessment, the Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD), Physician Global Assessment (PGA), Patient-Oriented Eczema Measure (POEM), and the pruritus Numerical Rating Scale (NRS) (Table 2).

BSA is used to assess dermatalogical conditions such as psoriasis and atopic dermatitis. Clinicians frequently use the percentage of total BSA affected (0%-100%) to assess the extent of disease. BSA estimates are also used to select patients for clinical trials. The EASI is a measure used to rate the extent and severity of atopic dermatitis across 4 body regions—the head and neck, the trunk, and the upper and lower extremities. It centers on 4 key clinical symptoms of atopic dermatitis: erythema (redness), induration/papulation (thickness), excoriation (eg, scratching), and lichenification. A modified EASI (mEASI) that incorporates patient pruritus reporting has been used in clinical trials. The presentation of severe atopic dermatitis is captured in the Image of a young man with a baseline BSA of 68.5% and an EASI of 42.0.

The SCORAD accounts for the extent and severity of signs of the disease (of dryness, lichenification, erythema, oozing/crusting, excoriation, and edema/papulation) and considers patient-reported outcomes (for sleep loss and pruritus). Adaptations of the SCORAD include the Patient-Oriented SCORAD (PO-SCORAD), which patients complete, and the objective SCORAD (oSCORAD), which excludes the patient-reported elements.

The US Food and Drug Administration (FDA) introduced the concept of a Physician Global Assessment in 1998; it has since recommended the use of a global assessment for primary end points in atopic dermatitis clinical trials. Many scales referred to by the terms "Investigator('s) Global Assessment" (IGA), "Physician('s) Global Assessment" (PGA), and "Physician('s) Global Evaluation" (PGE) have been used to assess atopic dermatitis severity in clinical trials. However, these scales differ widely, and this variety has...
Table 2. Select Clinical Outcomes Measures in Atopic Dermatitis1,2,11-13,15,35,36,42-46

<table>
<thead>
<tr>
<th>Clinical outcomes measure</th>
<th>Description</th>
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<tbody>
<tr>
<td>Body surface area (BSA) assessment</td>
<td>Percentage of BSA affected (0%-100%) is used to assess disease extent. BSA is a common measure in clinical practice and has also been used for clinical trial patient selection. BSA assessment is not standardized.11,12</td>
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<tr>
<td>Eczema Area and Severity Index (EASI)</td>
<td>Used to rate disease extent and severity. Focuses on 4 body regions7,42, centers on 4 key clinical symptoms.42</td>
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<tr>
<td>Investigator/Physician Global Assessment (IGA/PGA)</td>
<td>Many “Investigator(s) Global Assessment” (IGA), “Physician(s) Global Assessment” (PGA), and “Physician(s) Global Evaluation” (POE) scales have been used to assess atopic dermatitis severity in clinical trials.43,44 These scales vary widely in instructions, number of points used to rate each severity item, description and number of assessed items or symptoms, and use in analysis.43,45</td>
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<tr>
<td>Pruritus Numerical Rating Scale (Pruritus-NRS)</td>
<td>A measure whereby patients assess the severity of their itch. The Pruritus-NRS ranges from 0 (no itch) to 10 (the worst itch imaginable). Scores from 0 to 3 are considered mild in severity; 4-6, moderate; and 7-10, severe.2</td>
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<tr>
<td>SCORing Atopic Dermatitis (SCORAD)</td>
<td>A tool to measure the severity of atopic dermatitis. It is comprised of objective signs (disease extent and intensity) and subjective patient-reported symptoms (pruritus and sleep loss). Scores from 0-9.9 are considered clear.2 The system generates a composite score based upon a weighted index, with approximately 60% of the total score attributed to the intensity of lesions, 20% to the spread of lesions, and 20% to subjective symptoms as scored by the patient.2 Adaptations include Patient-Oriented SCORAD (PO-SCORAD) and the objective SCORAD (oSCORAD).11,15</td>
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<tr>
<td>Patient-Oriented Eczema Measure (POEM)</td>
<td>A patient or parent/caregiver-reported score relating to atopic dermatitis symptom severity and frequency and impact of treatment. Scores from 0-2 are considered clear/almost clear.2,38 POEM is used to assess 7 symptoms (itch, sleep, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the course of a week, with each symptom given equal weight.2</td>
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Challenges of Assessing Disease Severity

Although multiple disease severity assessments exist, each has its limitations.

As with psoriasis, BSA is not, in and of itself, a measure of disease severity for atopic dermatitis.11,12 Moreover, BSA assessment is not standardized, and the borders of lesions are often unclear, making BSA results variable.11,12 The EASI and SCORAD are useful in clinical trials, but they may be too time consuming to complete during clinical visits.2 The vIGA-AD poses a similar challenge: although it may ultimately replace the many IGA/PGA scales used in clinical trials, the vIGA-AD was not designed for clinical practice.11 The POEM and PO-SCORAD present a different challenge: although these tools allow physicians to evaluate the course of atopic dermatitis and the effects of treatment, they rely on patient report and are subjective in nature.2 Although the NRS-based instruments measure pruritus effectively, tools that assess more than just pruritus may gauge atopic dermatitis severity more dependably.14

There is a need for validated clinical tools to assess severity that use standardized definitions. The absence of such measures can impede meaningful comparison and synthesis of data and, in turn,
Informed clinical decision-making.15,16 Moreover, the use of adaptations like mEASI and oSCORAD may exacerbate confusion surrounding the interpretation of EASI and SCORAD results.15

The AAD guidelines recommend the use of objective and subjective tools to diagnose and assess the severity of atopic dermatitis.7 In the absence of a single disease severity measure that meets these criteria, providers should have the option to treat more severe disease using therapies best suited to the patient.

**GOALS OF THERAPY AND DISEASE MANAGEMENT**

Goals in the management of atopic dermatitis include controlling outbreaks and prolonging the time to next flare, managing comorbidities and secondary complications (e.g., infections), and minimizing adverse events, while trying to maximize positive outcomes.16 Key strategies include controlling inflammation, avoiding triggers, and strengthening the skin barrier.15

Basic nonpharmacologic measures are necessary across all severities of atopic dermatitis.1,15 These include daily bathing in water to hydrate the skin and remove scale, crust, irritants, and allergens.16 Hypoallergenic, fragrance-free, nonsoap cleansers are recommended for better tolerance.16 Liberal and frequent application of moisturizers is recommended to lessen the signs and symptoms of atopic dermatitis and reduce inflammation and severity.16 Additionally, patients are advised to avoid irritants or allergens, which include environmental triggers (e.g., changes in temperature and humidity, sweat, fragrances, wool).15 Antiseptic measures including diluted bleach baths and wet-wrap therapy may also be necessary to prevent infection.15,16

Topical therapies (e.g., over-the-counter topical corticosteroids [TCS]) should be introduced when good skin care and moisturizers no longer suffice for lesion control. TCS are used to address symptoms from acute flares and increase the time between chronic relapses.16,25 The potency and dose of TCS can be increased based on a single disease severity measure that meets these criteria, providers should have the option to treat more severe disease using therapies best suited to the patient.

Further pharmacologic treatment with existing and novel agents.15 Pharmacologic therapy selection should consider patient age, treatment history, atopy-related and atopy-unrelated comorbidities, treatment adherence concerns, and costs.1,15

The Atopic Dermatitis Yardstick, published in 2018, contains recommendations for the management of atopic dermatitis in clinical practice across all specialties.15 The recommendations follow current step therapy guidelines and focus on patients who have not responded to standard therapies or have greater disease severity.15 However, insurance requirements (e.g., use of specific documentation and severity measures) can limit provider access to the medications recommended in the yardstick and restrict appropriate therapy for patients.15

Management of atopic dermatitis requires a multifaceted approach to care.16 Given this and in the absence of reliable diagnostic biomarkers20 and a single appropriate disease severity measure, the management of atopic dermatitis among adult patients in the United States requires a treatment plan that considers both clinical outcomes and the patient’s QOL.15,17

**CONCLUSIONS**

The clinical and economic burden of atopic dermatitis is considerable. Moreover, the degree of pruritus and sleep disturbance posed by the disease greatly impact patient QOL. There is a need for easier ways to capture disease severity and to determine both how patients are doing on medication and which medications are most appropriate for each patient. Moreover, the complex pathogenesis, heavy burden, and limited diagnostic, staging, and therapeutic options available for advanced disease demonstrate that an individualized treatment plan is essential to optimize disease management of more severe atopic dermatitis among patients in the United States.21