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The Heterogeneity of Atopic Dermatitis

R. Chovatiya, MD, PHD[1], **J.I. Silverberg, MD, PhD, MPH**[2]

[1]Department of Dermatology, Feinberg School of Medicine at Northwestern University, Chicago, IL USA;

[2]Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC USA;

Abstract

Background: Recent advances were made in characterizing the clinical heterogeneity of atopic dermatitis (AD).

Objective: To review the clinical domains contributing to AD heterogeneity and describe their importance in clinical practice.

Methods: We conducted a focused review of the published literature, including retrospective, observational, and prospective studies, clinical trials, and consensus guidelines.

Results: AD is associated with heterogeneous skin manifestations, symptoms, lesional severity, lesional extent, longitudinal course, burden of signs and symptoms, and comorbidities. Each of these domains characterizes a different aspect of AD and should be used to guide overall severity assessment and clinical management. Primary focus on any one specific clinical domain of AD is insufficient to describe the full burden of disease.

Conclusion: Heterogeneity should be routinely considered during AD clinical encounters.

Keywords

atopic dermatitis; eczema; heterogeneity; burden

Corresponding author: Jonathan I. Silverberg, MD, PhD, MPH, The George Washington University School of Medicine and Health Sciences, Department of Dermatology, Suite 2B-425, 2150 Pennsylvania Avenue, Washington, DC 20037, JonathanISilverberg@Gmail.com, Twitter: @JonathanMD.

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Introduction

Atopic dermatitis (AD) is a chronic and burdensome inflammatory skin disease. Classically, AD is characterized as a relapsing, itchy, red, rash with a predilection for skin flexures, presenting mainly in childhood before "burning out" by adulthood. This narrow and overly simplified description overlooks the heterogeneity of AD. AD lesions have differing morphologies (e.g. prurigo nodules, lichenoid papules, follicular eczema) and distributions (e.g. extensor, head/neck, hand/foot).[1] While itch is the most prevalent and burdensome symptom of AD,[2, 3] skin-pain is one of several other symptoms that contribute to disease-burden.[4, 5] The course of AD is not homogenous – incidence, chronicity, and persistence vary widely over time.[6] This complex constellation of features poses physical, emotional, and psychosocial burden that contributes to reduced quality-of-life (QOL).[7, 8] Herein, we review clinical domains contributing to AD heterogeneity and discuss how balanced consideration of these aspects can improve AD management.

Skin Manifestations

The notion of a pathognomonic morphology and distribution of skin signs in AD, i.e. eczematous patches/plaques favoring flexural skin, has long been taught in dermatology. This view of AD is outdated, derived from older literature and anecdotal clinical experience of disease presentation in individuals of white race and Northern European ancestry, and ignores major differences in lesional morphology, distribution, and extent. Clinical presentation of AD varies widely across geographic regions, age,[9–11] ethnicity,[12] and underlying immunopathogenesis,[13] suggesting genetics[14] and environment[15] contribute to disease heterogeneity.

A systematic review and meta-analysis of 101 observational studies published from 1984–2017 underscored many regional and age-related differences in skin manifestations of AD.[1] Overall, lesions were distributed most commonly on flexural sites (58%), followed by extensor surface of upper extremities (51%), head, face, and neck (42%), hands and feet (36%), scalp (34%), and extensor surface of lower limbs (25%). Flexural involvement was more common in Australia, followed by Africa, Southeast Asia (SEA), East Asia (EA), and Europe, and less common in the Americas and Iran. Extensor lesions were most common in India, Iran, and EA. Head, face, and neck involvement was more common in Iran, Africa, and the Americas, and least common in SEA. Compared to European studies, truncal, extensor, scalp, and auricular involvement was more common in EA; head, face, and neck involvement was more common in Iran. Moreover, commonly reported morphological characteristics included perifollicular accentuation (follicular eczema; 34%), papular lichenoid (22%), nummular (13%), and prurigo lesions (7%). Papular lichenoid lesions, palmar hyperlinearity, orbital darkening, and ichthyosis were more prevalent in Africa. Dermatitis of eyelids, auricle, and ventral wrist, exudative eczema, and seborrheic dermatitis-like features were more common in children, while erythroderma, ichthyosis, palmar hyperlinearity, keratosis pilaris, hand/foot dermatitis, dyshidrosis, prurigo nodules and papular lichenoid lesions (features associated with chronic disease) were more common in adults.

A cross-sectional, US population-based study of adults with AD demonstrated heterogeneity of lesional distribution.[16] Only 40% of those with AD had active flexural lesions, of which 12.9% reported lesions only in these areas. AD lesions were quite symmetric and commonly involved the antecubital and popliteal fossae, lower legs, and dorsal feet. Truncal lesions were more common in blacks and Hispanics. Older age was associated with lesions on buttocks or genitals and less on face and scalp.

Symptoms

Symptoms contribute significantly to AD burden. Itch is the hallmark symptom of AD, being most prevalent, burdensome, and impactful on QOL.[2, 3, 17, 18] Skin pain, a previously under-recognized symptom, is also important in AD. Pain is a distinct symptom only weakly correlated with itch in AD[19]. Pain has heterogeneous frequency and intensity, increases with AD severity, and impacts QOL and mental health.[4, 5] Pain occurs even without excoriation, secondary to red inflamed skin (especially on face), skin fissures (especially on hands and digits) and less commonly with stinging from topical medications.[5] Many AD patients describe their skin pain using terms, e.g. “pinprick”, “electric shock”, and “stinging”, resembling neuropathic pain.[5]

Sleep disturbance is common in AD, especially with more severe disease.[20] AD is associated with fatigue limiting activities of daily living, regular daytime sleepiness, insomnia, feeling unrested, shorter sleep duration, trouble falling asleep, early-morning awakenings, and increased reports of sleep disturbances to clinicians.[21, 22]

Mental health symptoms (especially anxiety and depression) are also common among AD patients, though often go undiagnosed.[23–27] AD severity appears to be a major driver of these symptoms,[25] which in turn contribute to overall disease-burden.[28] Psychosocial distress in AD is higher than other chronic immune-mediated diseases, e.g. psoriasis, urticaria, asthma, and autoimmune disease.[29] Together, itch, pain, sleep disturbance, anxiety, and depression are all predictors of patient perception of their AD severity.[27]

Longitudinal Course

AD is a dynamic condition with longitudinal variation in persistence, signs and symptoms, and disease flares. A prospective study of US children with mild-to-moderate AD suggested that >80% of children have continued AD symptoms and/or medication use, with most not achieving a six-month disease-free period and only 50% achieving ≥1 disease-free period by age 20.[30] Several international studies estimated 40–60% persistence of AD beyond childhood.[31] A systemic review and meta-analysis provided more conservative estimates of persistence, with 80% of children with AD experiencing a period of observed disease clearance by age 8, and <5% having no disease clearance by 20 years after initial diagnosis.[6] Predictors of persistence into adulthood include more severe and early-onset AD, allergic multimorbidity, family history of atopic disease, urban environment, and filaggrin gene mutations.[32] Estimates of persistence in adulthood also vary across studies, but include many of the same predictors.[33–35] The relapsing-remitting nature of AD, punctuated by times of disease flare and quiescence, adds yet another dimension to the longitudinal

course of AD. Different patterns of AD activity include transient, early-onset-early-resolving (associated with favorable prognosis), early-onset-persistent and early-onset-late-resolving (associated with AD genetic risk scores and both personal and family history of atopy), mid-onset resolving, and late-onset resolving.[36]

AD signs and symptoms follow a unique longitudinal course. In a prospective clinical cohort study of adults with mild-severe AD undergoing standard-of-care treatment, most patients with mild disease had persistently mild AD, while those with moderate-severe disease either had more fluctuating or persistent improvement in severity over a two-year period.[37] Erythema and edema/papulation (acute or subacute signs)[38] showed the most fluctuation over time, while lichenification (a chronic sign)[38] and xerosis were more stable. These results suggest that chronic signs of AD are less responsive to treatment. Most AD patients had fluctuating itch and excoriation/scratching; fewer had persistent or improved excoriation/scratching.[39] Baseline excoriation severity was the strongest predictor of persistent excoriations. Patients with moderate-severe excoriations had the most fluctuation or sustained improvement while those with milder excoriations had persistently mild scratching severity. Itch and skin-pain also follow distinct courses, as itch fluctuated or persisted more, while skin-pain showed more sustained improvement over time.[19]

Comorbidities

Atopic comorbidities, including hay fever and food allergy, are strongly associated with AD[40–42] and are Hanifin-Rajka[43] and United Kingdom Working Party[44] diagnostic criterion. Shared epidermal-barrier abnormalities and type 2 immune skewing underlie these conditions.[45] AD severity is the strongest predictor of atopic comorbidities, though asthma (e.g., younger age, lower household income) and hay fever (e.g., older age, higher household income) have other unique associations.[42]

IgE-mediated food allergies are more common among infants and young children with moderate-severe AD. While diet restrictions are unlikely to resolve AD, food allergy testing is an important consideration among children with refractory AD, especially to identify those at risk of anaphylaxis.[46] Atopic keratoconjunctivitis may be more common among AD patients than previously believed and is associated with several ocular manifestations including potential blindness.[47] AD is associated with a higher likelihood of allergic contact dermatitis, likely through a combination of skin-barrier dysfunction, frequent application of topical medications, and heightened immune reactivity to transcutaneous irritants and contact allergens.[45]

AD symptoms, patient-burden, and neuro-inflammation may contribute to increased prevalence of mental health disorders in AD patients, including anxiety, depression, suicidality, and attention deficit (hyperactivity) disorder (ADD/ADHD).[48–50]

Skin-barrier dysfunction, decreased antimicrobial peptides, immune dysregulation, bacterial dysbiosis (with increased colonization by pathogenic bacteria), and chronic use of immunosuppressive medications[51] may contribute to increased cutaneous[52, 53] (bacterial,

viral, and fungal) and extracutaneous[54] (otitis media,[55, 56] sepsis,[52, 57] endocarditis,[52, 57] and bone and joint infections[52, 57]) infections in AD patients.

Treatment Approach

AD treatment guidelines recommend a step-up approach to therapy based on AD severity using both non-pharmacologic and pharmacologic interventions.[58–63] Approaches to severity assessment for treatment stratification varies based on practice guidelines. For general management, American Academy of Dermatology (AAD) recommends against using available AD severity scales in routine clinical practice and instead encourages general questions about AD signs, symptoms, course, and QOL impact.[64] In contrast, European Task Force on AD relies on SCORAD (includes lesional severity, extent, and severity of itch and sleep disturbance) to stratify AD severity.[62] Basic management of AD across all severities focuses on non-pharmacologic interventions that can be grouped into three major categories: optimized bathing, regular moisturization, and trigger avoidance (i.e., environmental modification to avoid proven allergens, irritants, etc.).[58, 59, 62] In mild AD, low-moderate potency topical corticosteroids (TCS) should be applied once-twice daily to active areas of eczema, often up to one week beyond clearance.[58, 59, 62] Topical calcineurin inhibitors (TCI), phosphodiesterase-4 inhibitors (e.g., crisaborole), or topical janus kinase (JAK) inhibitors (e.g., ruxolitinib) can also be considered. In moderate AD, TCS strength should be increased to medium-high potency, with similar consideration for non-steroid alternatives. Maintenance (i.e., “proactive”) therapy may be useful for these patients and consists of regular application of topical anti-inflammatories 1–3 times weekly to areas prone to flaring in order to prevent flares.[58, 60] In moderate and severe AD, specialist referral (e.g., dermatologist) is critical for consideration of advanced therapies, which include phototherapy, systemic immunosuppressants (e.g., cyclosporine A, methotrexate, mycophenolate mofetil, azathioprine), biologics (e.g., dupilumab, tralokinumab), oral JAK inhibitors (e.g., abrocitinib, baricitinib, upadacitinib), and in certain cases, wet-wrap therapy or inpatient hospitalization.[58, 61, 63] Despite their frequent use for management of moderate-severe AD, systemic corticosteroids are discouraged as chronic treatment given broad systemic side-effects associated with chronic use and risk of rebound flares.[61] Systemic corticosteroids may be used as a bridge to better long-term therapy or short-term rescue in severe, acute flares. Data support using certain adjunct therapies to treat AD comorbidities at all severities (e.g., oral antihistamines for allergic disorders, antibiotics for infections), while other interventions (e.g. complementary and alternative medicine, probiotics, specialized diets) lack well-controlled studies.[60, 63]

Incorporating AD Heterogeneity into Clinical Practice

No single clinical domain fully captures the heterogeneity of AD. Primary focus on any one disease aspect is insufficient to characterize AD activity, select therapy and monitor treatment response.

For example, a fully clothed patient can display only mild lesional severity on exposed areas of skin. However, a full skin examination may reveal a BSA of >50%, suggesting a more active disease state when lesional extent is assessed alongside severity. Alternatively, some

patients may have localized mild lesions but experience constant, severe itch, suggesting more severe AD when symptoms are incorporated.

A patient with thicker scaly plaques involving BSA of 5% may be classified as having mild AD based on lesional extent. However, lesions localized to hands and feet can be associated with intense cracking, bleeding, itch, pain and patient-burden during flares. In these circumstances, additional consideration of skin manifestations, symptoms, lesional severity, and burden of signs and symptoms would alter treatment considerations.

Patients with clear skin and minimal xerosis presenting in wintertime might be viewed as having inactive AD based on assessment of skin manifestations and lesional severity alone. However, such patients may have seasonally severe AD with summertime flares. Consideration of the longitudinal AD course is needed to appropriately tailor treatment.

Patients with localized, flexural eczema might be classified as having good control on topical therapy based on skin manifestations. However, thorough review of symptoms may reveal seasonal rhinosinusitis (i.e., hay fever) associated with clinically significant eyelid dermatitis, difficulty breathing with exercise (i.e., asthma), several food allergies with some foods possibly worsening their AD. In this circumstance, investigation of comorbid health conditions reveals untreated atopic multimorbidity, which is important for patients' overall health and may be directly relevant to their AD management.

Patients with skin of color may present for management of newly diagnosed AD and be classified as having relatively mild disease given minimal itch, clear flexures, and absent erythema, edema, or lichenification. However, a thorough total body skin exam may in fact reveal widespread follicular papules on the trunk, prurigo nodules on the legs, and widespread purple or brown patches/plaques. Special attention to unique skin manifestations across diverse patient populations indicates this is a patient with severe uncontrolled AD. These examples highlight some common scenarios in which appreciation of AD heterogeneity can guide care and facilitate successful outcomes.

Conclusion

AD is associated with heterogeneous presentation, treatments, and outcomes. Our understanding of AD manifestations, symptoms, severity, extent, course, burden and comorbidities has evolved significantly. Future efforts are needed to incorporate these clinical domains into a standardized framework that can be used in day-to-day practice to aid in diagnosis, assessment of disease activity, and ultimately, identification of relevant therapeutic subsets.

Conflicts of interest:

Raj Chovatiya reports personal fees from Abbvie, Incyte, Regeneron, and Sanofi-Genzyme. Jonathan Silverberg reports personal fees from Abbvie, Afyx, Arena, Asana, BioMX, Bluefin, Bodewell, Boehringer-Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo, Luna, Menlo, Novartis, Pfizer, RAPT, Regeneron, Sanofi-Genzyme; institution received grants from Galderma.

Abbreviations used:

AD	atopic dermatitis
DALY	disability adjusted life year
EASI	Eczema Area and Severity Index
QALY	quality adjusted life year
IGA	investigator's global assessment
QOL	quality of life
HRQoL	health-related quality of life
SCORAD	SCORing Atopic Dermatitis

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