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 ORIGINAL ARTICLE

Atopic Dermatitis: A Review of Current Diagnostic Criteria and a Proposed Update to Management

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ABSTRACT

The diagnosis of atopic dermatitis (AD) remains primarily a clinical diagnosis, in which several clinical signs and symptoms including pruritus, the presence and location of skin lesions, and a personal or family history of atopic conditions are used to facilitate a diagnosis. In recent decades, several well-established sets of criteria have been developed to aid diagnosis. With increased awareness of AD and the recent development of systemic immunomodulators to treat the condition, there exists a need to further define and consolidate the current diagnostic criteria while refining our current understanding of the clinical features of AD. We propose a novel, simplified set of criteria that comprises the clinical features generally considered to be essential for a confirmed diagnosis of AD, together with features previously regarded as having less clinical significance. It is essential, however, that any refinements to the diagnostic criteria for AD are made alongside regular updates of treatment guidelines so that these also reflect current developments. In this regard, the current guidelines in the United States are lacking and should be updated.

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INTRODUCTION

Atopic dermatitis (AD) is a common and chronic inflammatory skin disease characterized by intense pruritis, recurrent eczematous lesions, xerosis, and lichenification.[1,2] Although primarily recognized as a childhood disorder, starting in infancy and affecting up to 20% of children, AD is also prevalent in adults. Some adults may develop new-onset AD, while others may have recurrence of childhood AD symptoms that had shown remission. Using the strictest diagnostic criteria (age of onset <2 years old), a recent study indicated that the prevalence of AD among adults in the United States (US) is 7.3%.[3] In another study it was found that approximately 25% of adults with AD in the US have severe disease.[4]

Several sets of diagnostic criteria for AD have been described in recent decades; none are used universally, and each varies in the diagnostic features given prominence, thus precluding comparability between epidemiological studies.

The objective of this review is to describe the current thinking on the clinical features of AD alongside current treatment guidelines, in order to consolidate and distill past and current criteria used in AD diagnosis, and thereby propose a more simplified set of diagnostic criteria.

Clinical Features and the Diagnosis of AD

In the absence of a definitive laboratory test, a diagnosis of AD is made based on the presence and distribution pattern of lesions with specific morphologic features, associated clinical findings, and a personal or family history of atopy. Clinical features typically present are listed in Table 1.[5]

Many of the more recently described clinical features of AD such as baseline ocular features, periorbital dermatitis, and prurigo/prurigo nodularis[2,6,7] are now considered to hold greater clinical significance than previously assumed yet are lacking in older criteria that are still in routine use.

Further complicating a confirmed diagnosis of AD with a given set of criteria is the fact that several of the clinical features used in diagnosis are heterogeneous in nature, varying by global region and age.[2] Furthermore, phenotypic differences exist between adult- and childhood-onset AD; for example, a US study suggests that those with adult-onset AD are more likely to have been born outside of the US, have less atopy, and a predilection for hand, head, and neck rash than children with AD.[7] Such phenotypic differences should be considered in both diagnosis and when assessing disease severity.[2]

Current and Past Diagnostic Criteria

Hanifin–Rajka Criteria

The most widely used and recognized criteria for the diagnosis of AD are the Hanifin–Rajka criteria, introduced in 1980,[8] which remain one of the primary criteria used in the hospital setting today. This model mandates that at least 3 of 4 major

TABLE 1.

AAD Criteria vs Simplified 2-Plus-1 Criteria: Clinical Features to Consider in the Diagnosis of AD

	AAD Criteria[5]	2-Plus-1 Criteria
Essential features	Must be present • Pruritus • Eczema (acute, subacute, chronic) - Typical morphology and age-specific patterns[b] - Chronic or relapsing history	2 Must be present • Pruritus • Eczema (acute, subacute, chronic)[a] - Typical morphology and age-specific patterns[b] - Chronic or relapsing history
Important features Seen in most cases; adds support to the diagnosis	• Early age of onset • Atopy - Personal and/or family history - IgE reactivity • Xerosis	1 Must be present • Can be present at any age • Atopy - Personal and/or family history - IgE reactivity • Xerosis • Prurigo nodules • Periorbital eczema/eyelid dermatitis • Conjunctivitis not characterized as bacterial or viral • Other regional changes (eg, preauricular or periorbital changes)
Associated features Any of these can be present to aid in diagnosis; however, they are not distinguishable on their own for a definite diagnosis of AD	• Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response) • Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis • Ocular/periorbital changes • Other regional findings (eg, perioral changes/periauricular lesions) • Perifollicular accentuation/lichenification/prurigo lesions	• Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response) • Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis • Ocular/periorbital changes • Other regional findings (eg, perioral changes/periauricular lesions) • Perifollicular accentuation/lichenification/prurigo lesions
Exclusionary features A confirmed diagnosis of AD depends on the exclusion of these conditions	• Scabies • Seborrheic dermatitis • Contact dermatitis (allergic or irritant) • Ichthyosis • Cutaneous T-cell lymphoma • Psoriasis • Photosensitive dermatoses • Erythroderma of other causes • Immune deficiency diseases	• Scabies • Seborrheic dermatitis • Contact dermatitis (allergic or irritant) • Ichthyosis • Cutaneous T-cell lymphoma • Psoriasis • Photosensitive dermatoses • Erythroderma of other causes • Immune-deficiency diseases (eg, HIV, severe combined immune deficiency, agammaglobulinemia, Wiskott-Aldrich syndrome, hyper-IgE syndrome) • Cutaneous tinea • Other spongiotic dermatoses (eg, atopiform dermatitis, dermatophytosis, Gianotti-Crosti syndrome (GCS) • Psoriasiform drug eruptions (eg, lichen planus)

Abbreviations: AD = atopic dermatitis; AAD = American Academy of Dermatology
[a]The timeframe for acute, subacute, and chronic essential features (The Rule of 6) should be as follows: acute: ≤6 weeks in duration; subacute: ≥6 weeks but not longer than 6 months in duration; chronic: ≥6 months in duration
[b]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.
Red text denotes newly proposed criteria

criteria be met along with at least 3 of 23 minor criteria. The major criteria are pruritus, typical morphology and distribution of the condition (ie, facial and extensor involvement in children; lichenification of flexural areas in adults), a chronic relapsing course, and a personal or family history of atopy. Validation studies of the Hanifin–Rajka criteria report sensitivity and specificity ranges of 87.9% to 96% and 77.6% to 93.8%, respectively.[9] Refinements of the Hanifin–Rajka criteria have been made over the years. Some reports have disputed the diagnostic significance of some of the 23 minor criteria,[10] while others have suggested that additional features should be included and that >3 minor features are normally present in a confirmed diagnosis.[11]

United Kingdom (UK) Working Party Criteria

Outside of the hospital environment, the Hanifin–Rajka criteria are difficult to interpret by the average dermatologist or primary care practitioner, which can result in inaccuracies in diagnosis and/or further treatment delays. Recognition of this led to the establishment of the UK Working Party criteria in

1994, a refined set of criteria developed by 13 dermatologists and practitioners.[12–14] Their aim was to condense the Hanifin–Rajka criteria into a core, sensitive, and specific set, suitable for non-dermatologists, and applicable to a range of ethnic groups. Furthermore, it was anticipated that these non-invasive criteria, with no requirement for laboratory testing, would be suited to the diagnosis of patients in both hospital and private settings.

The criteria consists of 1 mandatory criterion—pruritis—plus ≥3 of the following 5 major criteria: history of flexural involvement, history of dry skin, onset of AD <2 years of age, history of any other atopic condition (eg, asthma), and visible flexural dermatitis.[12] Validation of the criteria in dermatology patients provided a sensitivity and specificity of up to 85% and 96%, respectively.[14] A more recent systematic review of 19 studies, however, has reported that while specificity was similarly high, sensitivity varied widely—between 10% and 100%.[9]

Millennium Criteria

The Millennium criteria were first introduced in 1998 by Bos and colleagues, who sought to further distill and condense the Hanifin–Rajka and the UK Working Party criteria into a set that would identify and diagnose patients with true AD.[15] It was the first criteria to include the presence of allergen-specific IgE as a diagnostic feature.

Further refined and validated by Schram and colleagues in 2011,[16] the Millennium criteria mandate that ≥5 criteria are necessary to accurately identify AD patients: typical morphology, early age of onset, Dennie–Morgan infra-orbital skin fold, history of flexural involvement, and visible flexural eczema. The authors compared their refined criteria with the Hanifin–Rajka and UK Working Party criteria in a cohort of 210 outpatients for whom a diagnosis of AD was considered in the differential diagnosis. The Millennium criteria showed a sensitivity of 81.8% and a specificity of 98.8% compared with 100% and 48.8% for the Hanifin–Rajka criteria and 97.7% and 72.9% for the UK criteria, respectively.[16]

American Academy of Dermatology (AAD) Guidelines

In 2014, the AAD, the leading resource for dermatologists in the US, in conjunction with well-renowned experts in the field of AD, produced guidelines for AD diagnosis and assessment.[5] The guidelines describe the clinical features that should be considered when making a diagnosis and are classified into essential, important, and associated features (Table 1).

Essential features in the AAD guidelines are those that must be present for an AD diagnosis to be made, and include: pruritis, eczema, timeline of disease, morphology, and disease pattern/history (chronic or relapsing). Important features are those observed in most cases, lending support to AD as the diagnosis. These include early age of AD onset, a personal/family history of atopy and/or IgE reactivity, and xerosis. Associated features are those suggestive of disease but are considered too non-specific. The AAD consensus criteria also recommend that physicians exclude conditions that mimic AD when making a diagnosis; these exclusionary features include scabies, irritant or allergic contact dermatitis, seborrheic dermatitis, cutaneous T-cell lymphoma, ichthyoses, psoriasis, photosensitive dermatoses, erythrodermas, and immunodeficiency disorders (Table 1).

Current Treatment Guidelines for AD

The current US recommendations for the treatment of AD, developed by the AAD were last updated in 2014.[17,18] Topical agents form the basis of AD treatment. Non-pharmacologic approaches such as moisturizers, bathing practices, and wet wraps focus on moisturization and restoration of epidermal barrier function, with the aim of avoiding disease flares and the need for pharmacologic intervention.[17] Pharmacologic topical therapies include corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, antimicrobials, and antihistamines. Topical corticosteroids (TCS) are typically introduced after failure to respond to preventive measures and are often used alongside topical calcineurin/phosphodiesterase inhibitors to maintain remission. Although the incidence is low, both topical and systemic side effects can occur with TCS and this should be considered, particularly when treating children. Topical calcineurin inhibitors are particularly useful at sensitive sites, such as the face and skin folds, where there is a greater adverse risk profile with TCS.[17]

Patients whose AD is refractory to topical agents require systemic treatments. According to the AAD, these are indicated "for the subset of adult and pediatric patients in whom optimized topical regimens and/or phototherapy do not adequately control the disease, or when quality of life is substantially impacted."[18] While phototherapy is still used in certain cases, the more prevalent treatment options are systemic immunomodulatory agents. The AAD guidelines suggest that cyclosporine (level of evidence: BI-II), methotrexate (BII), mycophenolate mofetil (CIII), and azathioprine (BII) are more widely used and more efficacious than IFN-γ (BII) and oral calcineurin inhibitors.[18] The AAD guidelines recommend avoiding systemic steroids for the treatment of AD, stating that their use should be restricted for acute severe exacerbations and as a bridge therapy to another systemic, steroid-sparing treatment.[18]

Despite the ongoing development of immunomodulatory biologic agents specifically targeting the type 2 inflammation common to AD, biologics are not mentioned as a systemic treatment option in US guidelines,[19–21] though they are included in the most recent European guidelines.[22] There is an urgent need for the AAD to address this omission.

In 2017, an expert panel from the International Eczema Council proposed in a consensus statement that the decision to start

systemic treatment should depend not only on the disease severity but also on the psychologic needs of the patient and the risk–benefit ratio of the systemic therapy involved.[23] Surprisingly however, apart from dupilumab, the majority of systemic treatments most commonly used to treat AD in the US (methotrexate, cyclosporine, mycophenolate, and azathioprine) do not carry an approved label for that indication.[23] Moreover, despite its approval by the US Food and Drug Administration as the first biologic medication indicated for moderate-to-severe AD, dupilumab has yet to be listed on insurance plans as a first-line agent for these patients over the off-label alternatives.

In addition to the inclusion of newer treatments, the AAD treatment guidelines should be updated to reflect more accurately the risk–benefit profiles of the various recommended systemic immunomodulators. A recent study, for example, comparing methotrexate with cyclosporine in the treatment of moderate-to-severe AD revealed that despite its inferior efficacy (at lower doses only), methotrexate displayed a significantly favorable safety profile compared with cyclosporine.[24]

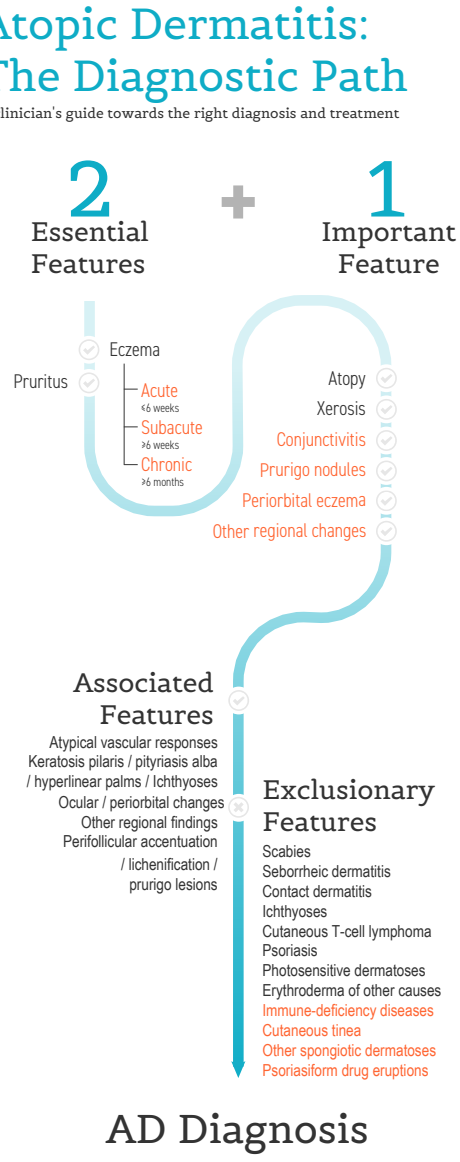
Once updated, physicians should be urged to review the guidelines regularly. This is particularly pertinent as a recent study assessing the adherence to evidence-based guidelines of care for AD in the US described an educational gap in the implementation of the current, albeit outdated, guidelines.[25]

Proposed Diagnostic Criteria for AD

Of all the existing diagnostic criteria, none are considered wholly or mutually exclusive in the diagnosis of AD; the clinician ultimately makes the final diagnosis. This lack of standardization has obvious implications on the comparability of research findings and was highlighted in a recent systematic review of the diagnostic criteria used in randomized controlled trials of AD.[26] In 212 trials examined, 10 different sets of criteria were used, with the Hanifin–Rajka criteria most widely used (in 41% of studies) and the AAD criteria used in only 3.8% of studies. Interestingly, no criteria were specified in 37.3% of the studies, and the authors concluded that there was a need for a harmonized set of diagnostic criteria.

We propose a simplified model consisting of the essential features of the more widely used diagnostic criteria, clarifying the duration and age at onset of the features. Importantly, these criteria include the newer features of AD such as conjunctivitis, periorbital dermatitis, and prurigo/prurigo nodularis, that were previously regarded to have relatively little significance in the context of the overall disease. Our model also proposes clear definitions for the acute (≤6 weeks), subacute (≥6 weeks but not longer than 6 months), and chronic (≥6 months) classifications of AD. For comparison, our proposed 2-plus-1 model is shown in Table 1 alongside the diagnostic criteria currently recommended by the AAD,[5] and in Figure 1.

FIGURE 1. 2-Plus-1 AD diagnostic criteria. A quick reference guide for clinicians diagnosing AD based on the 2-plus-1 criteria. The updated criteria are in red. Abbreviation: AD = atopic dermatitis



We believe that these simplified and updated criteria for the diagnosis of AD will aid dermatology and non-dermatology providers in establishing the diagnosis earlier, leading to a lower rate of misdiagnosis, earlier treatment, and fewer criteria requirements for payers to agree with providers in initiating systemic therapy options for patients.

CONCLUSIONS

In recognition of the need for the diagnostic criteria for AD to be updated, we propose a novel, simplified 2-plus-1 model that comprises essential and important features of the most widely used criteria while also emphasizing features previously considered to be of less clinical significance. This model also clarifies

the duration and age of onset of the essential and important features.

Subsequent treatment following a diagnosis of AD is reliant on treatment guidelines that reflect current knowledge. It is imperative, therefore, that AD treatment guidelines are updated regularly to reflect more accurately the risk–benefit profiles of systemic immunomodulators and to include newer treatment alternatives, particularly for moderate-to-severe AD cases. The advent of monoclonal antibodies aimed at targeting all aspects of the atopic disease spectrum may require us to revisit treatment algorithms, the implications of which would be far reaching, both for pharmaceutical drug development and in the establishment of guidelines for insurance-based drug formularies.

DISCLOSURES

Matthew Reynolds is a medical advisor and speaker for Sanofi and Regeneron; medical advisor for AbbVie Inc. and Eli Lilly and Company. Matthew Bruno is a medical advisor for AbbVie Inc., Dermira, Mayne Pharma, and PharmaDerm; and speaker and medical advisor for Almirall, S.A., Pfizer Inc., and Sun Pharmaceutical Industries Ltd. Joe Gorelick is a consultant, advisor, and speaker for AbbVie Inc., Beiersdorf, Celgene Corporation, Dermira, Eli Lilly and Company, Encore Dermatology Inc., Foamix Pharmaceuticals Ltd., LEO Pharma, Mayne Pharma, Novartis Pharmaceuticals, Ortho Dermatologics Inc., Primus Pharmaceuticals, PruGen Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Sanofi-Genzyme, Sun Pharmaceutical Industries Ltd., and UCB S.A.

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