



# Atopic dermatitis guidelines: Diagnosis, systemic therapy, and adjunctive care

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**Abstract** Atopic dermatitis is an important and chronic skin condition that has recently been the subject of enormous volumes of basic science, clinical, and epidemiologic research. This field is undergoing rapid expansion, making it vitally important to integrate the emerging data with our current body of knowledge. In 2014, the American Academy of Dermatology published Guidelines of Care for the Management of Atopic Dermatitis, composed of four parts, reflecting the work of 17 experts from North America and the United Kingdom.<sup>1-4</sup> It uses a patient-oriented system, SORT (Strength of Recommendation Taxonomy), to provide evidence-based guidance in the management of this common, vexing dermatitis. These guidelines join a series of similar efforts published recently across the world, reflecting universal interest in distilling the tremendous volume of basic scientific and clinical data previously generated.<sup>5-7</sup> With new therapies rapidly emerging, clinicians require a current understanding of the field to be able to incorporate new treatments in their practice. © 2018 Elsevier Inc. All rights reserved.

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Atopic dermatitis (AD) is often a diagnosis made by gestalt. It would be reassuring in some complicated cases and essential for clinical trials to have validated diagnostic criteria. A number of diagnostic schema were reviewed, beginning with the most time-honored Hanifin-Rajka criteria.<sup>8</sup> The expert panel (EP), organized by the American Academy of Dermatology, ultimately endorsed a modified version, utilized by the 2003 Consensus Conference, that is more streamlined and applicable to both children and adults.<sup>9</sup> (Table 1)

Another evaluation tool in the clinical care of AD patients would be a reliable biomarker that could aid both in confirming the diagnosis and tracking disease progress. The EP found no support for any specific biomarker in AD. Many of the

cytokines and chemokines recently identified in AD inflammation have become potential therapeutic targets, including TSLP<sup>10</sup>; IL-31, which seems specifically associated with itch,<sup>11</sup> and IL-4 and IL-13, the targets of dupilumab.<sup>12</sup> While filaggrin null mutations do tend to predict a more severe course of atopy,<sup>13</sup> testing is not yet routinely recommended. Though often used mistakenly for this purpose, the EP specifically warns against using serum immunoglobulin E levels for routine assessment.

Clinical associations with AD have greatly expanded in recent years. Current concepts are well beyond thinking solely of the “atopic march”:

- eczema and food allergies as an infant
- asthma as a child
- hay fever as an adult

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**Table 1** Atopic dermatitis diagnosis (adapted from Eichenfield et al<sup>1</sup>)

Essential features	
	Pruritus
	Typical morphology (eg, facial, extensor in infants, flexural in older children)
	Waxing and waning history
Important features	
	Early onset
	Personal or family history of atopic conditions (eg, asthma, allergies, hayfever)
	Immunoglobulin E hyperreactivity
	Xerosis
Associated features	
	Upper lip cheilitis
	Nipple eczema
	Atypical vascular responses (centrofacial pallor, white dermographism)
	Keratosis pilaris, pityriasis alba, ichthyosis vulgaris, palmar hyperlinearity
	Ocular/periorbital changes
	Perifollicular accentuation/ lichenification/prurigo lesions

Rule out clinical mimics, including scabies, seborrheic dermatitis, contact dermatitis, primary immunodeficiency, psoriasis, ichthyosis, lymphoma, dermatomyositis

Sleep disruption, which occurs in up to 60% of children with AD,<sup>14</sup> was highlighted, as were more recently described links such as attention-deficit/hyperactivity disorder.<sup>15</sup> Additionally, depression has been increasingly described in children and adults<sup>16</sup>; obesity has also been described as overrepresented in AD cohorts.<sup>17</sup> (Figure 1)

Since the publication of these guidelines, considerable additional work has been done to identify gaps and comorbidities,<sup>18</sup> to the extent that it has become challenging to establish a point of emphasis. The recommendation of the EP still rings true: “an integrated, multidisciplinary approach to care may be valuable and is supported for AD patients who present with common associations.”<sup>1</sup>

## Phototherapy and systemic therapy

Phototherapy and systemic therapy are evolving so rapidly that guideline obsolescence may come most quickly. For example, 2014 seems an eternity ago, when new Phase 3 trials germane to AD care were being published seemingly on a monthly basis. The pipeline for AD drugs has never been so

### Established

Food allergy

Asthma

Seasonal allergies

Sleep loss

Pain

Skin infections

Contact dermatitis

### Emerging

Attention deficit hyperactivity disorder

Obesity

Anemia

Alopecia areata

Vitiligo

Cardiovascular disease

Lymphoma

Headaches

Autism

Speech disorders

Henoch Schonlein purpura

Basal cell carcinoma

**Fig. 1** Atopic dermatitis comorbidities.

**Table 2** Systemic agents for AD (adapted from Sidbury et al<sup>3</sup>)

Drug	Dosing	Onset of action	Comments
Cyclosporine	150-300 mg/d Pediatric: 3-6 mg/kg/d	1-4 weeks	Monitor blood pressure, renal and liver function, CBC, Mg, uric acid Tuberculosis (Tb) test Pregnancy, HIV if indicated
Methotrexate	7.5-25 mg/week Pediatric: 0.2-0.7 mg/kg/week	4-8 weeks	CBC, liver and renal function Tb test Pregnancy, HIV if indicated
Mycophenolate mofetil	1.0-1.5 g PO twice daily Pediatric: 30-50 mg/kg/d	4-8 weeks	CBC, liver function Tb test Pregnancy, HIV if indicated
Azathioprine	1-3 mg/kg/d Pediatric: 1-4 mg/kg/d	4-8 weeks	CBC, liver, renal function Tb test Pregnancy, HIV if indicated

replete. The most exciting advance does postdate the guidelines; ie, the SOLO1 and SOLO2 experience with dupilumab in Phase 3 trials.<sup>12</sup> As newer agents are developed, dermatologists should not abandon drugs known to help patients.

- They have a longer safety track record by definition.
- New drugs will be expensive and not accessible to all.

The EP found insufficient comparative data to recommend a single agent as first line for moderate to severe AD patients. A helpful set of considerations was outlined,<sup>3</sup> (Table 2) including when systemic agents are appropriate to consider. The group emphasized that the following conditions must be in place:

- Diagnosis assured, including the ruling out of allergic contact dermatitis and mycosis fungoides, where appropriate
- Elimination or minimization of all identifiable triggers
- Assured compliance with topical and/or phototherapy
- Optimized topical regimen, including wet wraps where possible

Once the need for a systemic agent has been established, there are little comparative data to discriminate among four systemic agents:

1. cyclosporine
2. methotrexate
3. mycophenolate mofetil
4. azathioprine

Each of these agents has been shown to be effective, and each has its own unique panel of concerning adverse effects. Among the EP, cyclosporine was the agent used most frequently, most likely due more to its rapid onset of action than to superior efficacy or safety. This preference has recently been supported by the Pediatric Dermatology Research Alliance survey study<sup>19</sup>; however, the literature is mixed in suggesting it is more effective, with some evidence that other agents may have a more durable effect.<sup>20</sup> The best

recommendation is to individualize therapy based on options available, risk-benefit analysis, and parent/patient preference. The guidelines include tables that describe interactions, toxicities, contraindications, and monitoring schedules, which should be particularly useful to physicians who do not routinely utilize these agents.

Other adjunctive therapies, such as antimicrobials and antihistamines, are also discussed. The literature does not support the use of omalizumab, oral calcineurin inhibitors, and intravenous immunoglobulin. Narrow-band ultraviolet B is considered first-line phototherapy due to its ease of use, efficacy, and relative safety profile, but other modalities, including home treatment, are described.<sup>21-23</sup>

## Adjunctive therapies

A vexing clinical question has long been how best to prevent disease flares. The EP first encountered a related dilemma: How to define them? There is tremendous variability across the literature as to what constitutes a flare:

- increased itch?
- worsening dermatitis?
- increased demand for medication?

The truth is all of the above, of course, and intuitively, it is not difficult at all for a patient, parent, or physician to recognize a flare, but defining the flare for clinical investigation remains challenging. With this caveat, two different but reproducibly successful approaches were highlighted in these guidelines:

- the role of education
- proactive use of prescription topical corticosteroids and calcineurin inhibitors

It should come as no surprise that in a condition characterized by misinformation and opinion-driven care, interventions aimed at improving the patient understanding of best practices

would be successful. Numerous studies from diverse populations have now shown that therapeutic education targeted toward the patient and/or caregiver may be the most effective therapy for AD. Therapeutic education is also likely the most cost-effective and certainly the safest. The best support for this approach comes from day treatment programs, or “eczema schools,” more common in Europe, where consistently better outcomes have been correlated with educational intervention.<sup>24,25</sup>

Another approach involves using online resources,<sup>26</sup> which allows brief appointment times to be leveraged and “extended.” These online AD-related resources include a wide array of topics, such as wet wraps and bleach baths (eg, [www.eczemacenter.org](http://www.eczemacenter.org)). These videos can be accessed as part of the clinic visit or recommended for home viewing.

Detailed algorithmic “eczema action plans” may simplify an otherwise daunting set of instructions for both patients and parents.<sup>27,28</sup> The details of these plans may be provider-dependent, but the key is written information, allowing both parents and patients to respond in real time as AD inevitably waxes and wanes.

The concept of proactive therapy with topical prescription medications is also highlighted. The timeworn AD treatment strategy has encouraged the use of topical steroids or calcineurin inhibitors when the skin is inflamed, with emollients alone when redness and itch abate. This can be an effective strategy and is grounded in the need to introduce “breaks” from medications to avoid adverse effects. For some patients, the inevitable recurrence of the dermatitis and sense of “chasing the eczema” can be frustrating. In addition, some patients find the breaks are increasingly difficult to achieve with concerns for overuse of medications.

While AD remains mysterious in many ways, one of those ways is not where the dermatitis will recur. Most patients know exactly where they will flare, whether it is the antecubital fossa or elsewhere. “Proactive therapy,” as recommended in the AD guidelines, consists of “continued use of either topical corticosteroids 1-2 times per week or topical calcineurin inhibitors 2-3 times per week after disease stabilization to previously involved skin, to reduce subsequent flares or relapse.”<sup>2</sup> Safety studies utilizing this approach do not extend past 12 months, nor is it clear which patients might optimally benefit from this type of regimen, but this proactive approach offers potential for flare reduction.<sup>29</sup>

Part IV of the guidelines also tackles the challenging relationship between dermatitis and food allergies. At its most basic, the question boils down to one posed in the title of a 1995 manuscript by Halbert et al: “Atopic dermatitis—an allergic disease or a disease with allergies?”<sup>30</sup> Two decades hence, we have still not answered this question. Perhaps more than any other aspect of AD care, this confusion can lead to harm through malnutrition due to food fear or faddism. The guidelines emphasize the helpful effort of the National Institute of Allergy and Infectious Diseases in 2010.<sup>31</sup> A diverse expert panel consisting of allergists, dermatologists, pediatricians and others convened to offer evidence-based guidance. While

the document addresses food allergy questions well beyond their relationship with eczema, this question is addressed in depth. The entire document is more than 50 pages long, but there are useful “digested” versions for both providers and parents/caregivers that can offer far more information than can possibly be covered in a 10- to 20-minute office visit. The single most useful recommendation from these guidelines relates to allergy testing. There is often a push from parents and even primary care providers to test broadly to “get at the root cause.” This is not always helpful. The NIAID recommendation states: Consideration of limited food allergy testing (ie, cow’s milk, egg, wheat, soy, peanut) if a child <5 years of age has moderate to severe AD and the following:

- persistent disease in spite of optimized management and topical therapy
- a reliable history of an immediate allergic reaction after ingestion of a specific food
- or both<sup>32</sup>

Embedded in this recommendation is the idea that an allergy test result is simply that: a test result not an allergy. An actual food allergy requires a clinical reaction and/or history to go along with that result. This gets at the idea of taking a good history—the best allergy “test” of all—as well as the concept of false positives (and less commonly negatives) that can be so stressful for parents (when their child tests “positive to everything”). The evolving story of early peanut exposure to prevent peanut allergy has prompted this National Institutes of Health (NIH) panel to append the 2010 guidelines to specifically accommodate these fascinating new data.<sup>33,34</sup> In children at risk for peanut allergy, defined in the seminal study as having either a history of dermatitis, egg allergy, or both, calibrated exposure to age-appropriate peanut protein between 4 and 11 months is indicated to decrease the risk of developing peanut allergy. The protocol for introduction depends on individual patient characteristics. Management of immunoglobulin E-mediated allergies with an allergist is generally indicated.

The guidelines close by reviewing the long list of adjunctive, complementary, and alternative interventions that have been tried and/or studied as treatment or prevention of AD. The level of evidence ranges from modest/mixed (eg, probiotics, vitamin D)<sup>35,36</sup> to nonexistent.<sup>37</sup> The continued widespread use of such interventions despite this underwhelming evidence base is yet further testimony to the need for better AD education.

## Conclusions

The 2014 American Academy of Dermatology Guidelines are a valuable, comprehensive review of the current state of AD care. Since their publication, there have been over 1000 additional citations in PubMed relating to AD, including some pivotal Phase 3 clinical trials. Advances in the basic

understanding of AD pathophysiology will continue to provide a roadmap for new targeted therapies, while greater insight into the burden of disease and comorbidities reminds us why better treatments are so essential.

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