

Original article

Consensus guidelines in diagnosis and treatment of atopic dermatitis

Atopic dermatitis is a common condition of great health significance. Consensus-driven guidelines of care or specific practice parameters may be useful, as are treatment algorithms based upon disease severity. Development of consensus guidelines on diagnosis and treatment of atopic dermatitis are discussed, and disease-severity-based guidelines of care proposed.

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In atopic dermatitis, consensus-driven guidelines of care or specific practice parameters have not been available. Diagnosis of atopic dermatitis is not a difficult process, though schema for acceptable diagnosis are not internationally accepted, and different diagnosis criteria may be more useful for some functions than others, including clinical trials, epidemiologic studies, or clinician training. Several useful scoring systems exist for assessment of disease severity, though none emphasizes the differences in disease burden over time (persistent disease, frequently recurrent disease *vs* disease with long remissions). Finally, there are no consistent guidelines on treatment of atopic dermatitis based upon disease severity. This paper will review recent work on establishing consensus guidelines on atopic dermatitis, and proposes disease-severity-based guidelines of care for atopic dermatitis treatment.

Three recent documents reflect attempts to evaluate atopic dermatitis and develop consensus guidelines. The American Academy of Dermatology Consensus Conference on Atopic Dermatitis (1), The International Consensus Conference on Atopic Dermatitis II (ICCAD II) (2), and The American Academy of Dermatology Guidelines of Care for Atopic Dermatitis (3) are important steps forward in defining issues of relevance for

individuals interested in atopic dermatitis research and care. Another important resource is the summary of the evidence supporting efficacy and safety of standard treatments of atopic dermatitis compiled by the Cochrane group (4).

American Academy of Dermatology Consensus Conference on Atopic Dermatitis

The American Academy of Dermatology (AAD) held a Consensus Conference on Atopic Dermatitis in 2001, published in late 2003 (1). The conference was based on the premises that:

- Current information identifying risk factors for atopic dermatitis in childhood was limited.
- Cutaneous disease prevention programs and health promotion strategies in children and adolescents had not been addressed in a concerted way by government agencies or relevant medical societies.
- Disease-based interventions often emphasized adult disease, but more effective strategies to prevent or minimize atopic dermatitis and allergies may require intervention during childhood years.

- Research may be more effectively co-ordinated and carried out with the establishment of consensus on how best to diagnose and treat diseases such as atopic dermatitis in children and identify the most critical issues related to this condition.

The conference was tasked with defining the core dermatologic issues related to atopic dermatitis in children and adolescents which can influence their dermatologic health over a lifetime; and prioritize future research efforts on epidemiology, pathogenesis, prevention and management of atopic dermatitis.

Highlights from the conference include a simplified system for defining atopic dermatitis as a syndrome. Essentially a revision of the Hanifin–Rajka criteria, the clinical findings that define the syndrome are divided into essential features, important features seen in most cases, and associated features which help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research or epidemiologic studies (Fig. 1).

Determination of disease severity is addressed. The consensus paper states that the Eczema Area and Severity Index (EASI) system and the Severity Scoring of Atopic Dermatitis (SCORAD) system are two systems that appear to be the most reliable and user-friendly and share the advantage that they are most commonly employed in contemporary clinical trials (5,6). Both systems are useful because they generate quantifiable data that are amenable to analysis, with the EASI system

Atopic dermatitis (AD) is best viewed as a syndrome. Clinical findings that define this syndrome and clinical criteria of AD include:

A. Essential features (must be present):

1. Pruritus
2. Eczema (acute, subacute, chronic)
 - a. Typical morphology and age-specific patterns*
 - b. Chronic or relapsing history

*Patterns include: i) facial, neck and extensor involvement in infants and children; ii) current or prior flexural lesions in any age group; iii) sparing of groin and axillary regions

B. Important features (seen in most cases, adding support to the diagnosis):

1. Early age of onset
2. Atopy
 - a. Personal and/or family history
 - b. IgE reactivity
3. Xerosis

C. Associated features (these clinical associations help to suggest the diagnosis of AD but are too nonspecific to be used for defining or detecting AD for research or epidemiologic studies):

1. Atypical vascular responses (e.g. facial pallor, white dermographism, delayed blanch response)
2. Keratosis pilaris/hyperlinear palms/ichthyosis
3. Ocular/ periorbital changes
4. Other regional findings (e.g. perioral changes/periauricular lesions)
5. Perifollicular accentuation/lichenification/prurigo lesions

Exclusionary conditions: It should be noted that a diagnosis of AD depends upon excluding conditions such as: scabies, seborrheic dermatitis, allergic contact dermatitis, ichthyoses, cutaneous lymphoma, psoriasis and immune deficiency diseases.

Figure 1. Clinical findings that define atopic dermatitis. From: Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB Consensus conference on pediatric atopic dermatitis. J Am Acad Dermatol. 2003 Dec;49:1088–95.

generating a composite score, whereas the SCORAD system picks a specific area of the body to be assessed. Both systems are considered to have merit, are reasonably reproducible, and are viewed as complementary methods by which to gauge efficacy. It is suggested that quality of life issues should be considered as well.

The immunologic, biochemical and other pathogenic mechanisms of atopic dermatitis are summarized as a complex interplay of numerous elements including immune, genetic, metabolic, infectious and neuroendocrine factors, and their interaction with the environment, with a statement that even an introductory discussion of this topic was beyond the scope of the paper. Factors that may be important in atopic dermatitis are listed, genetic influences on atopic dermatitis are briefly discussed, and goals are proposed for future research.

One of the four sections of the consensus conference reviews atopy, allergen exposure and the development of atopic dermatitis. The paper states that the influence of maternal food intake and infant feeding patterns on atopic dermatitis development is a complex issue. Food allergies are more common in children with established atopic dermatitis than in nonatopic children, and immunoglobulin E (IgE) -mediated sensitization is demonstrable in the majority of, but not all, atopic dermatitis patients, by methods which include skin prick tests, specific IgE antibodies and allergen patch tests. Concordance of sensitization with food and aeroallergens with the development of atopic dermatitis has been shown in prospective studies, but specific cause and effect relationships have not been convincingly displayed. The paper concludes that there is uncertainty of how exposure, or the timing of exposure, of allergens *in utero* or afterwards may influence the development of atopic dermatitis, and also uncertainty of the utility of allergen avoidance in unselected populations of children with atopic dermatitis.

The consensus paper also states that data are inconsistent on the impact of infant feeding patterns on the development of atopic dermatitis, and that there is no consensus regarding feeding recommendations. Allergen sensitivity is recognized as a trigger to atopic dermatitis in a subset of children with atopic dermatitis. Food allergies in atopic dermatitis patients may induce eczematous dermatitis in some, or urticarial reactions, contact urticaria, or other noncutaneous symptoms. The section ends with recommendations on future research on atopy, allergens and atopic dermatitis, including: a prospective study correlating longitudinal history of atopic dermatitis with allergen sensitization and laboratory data (e.g. CAP-RAST®, Pharmacia); studies on the impact of early treatment and consistent disease control on the course of atopic dermatitis and the progression of atopy; and studies on specific allergen avoidance.

The final section of the consensus conference deals with treatment of atopic dermatitis. The evidence basis for standard treatment options is reviewed, including

bathing, emollients, topical corticosteroids, and topical nonsteroidal immunomodulatory agents (calcineurin inhibitors). Emollients are considered to be effective first-line agents in the management of atopic dermatitis and may be steroid-sparing. Low- and mid-potency topical corticosteroids are discussed as first-line therapy disease exacerbations. In general, these agents are applied twice daily to induce control of inflammation (some preparations may be used once daily); there is no evidence that more frequent application enhances efficacy. Once disease activity is controlled, topical corticosteroids should be used intermittently. The least potent preparation that adequately controls the disease process should be selected. Once disease control is achieved, the topical corticosteroid should be tapered to a less potent preparation or withdrawn. When selected and used appropriately, these agents are not associated with significant adverse effects (e.g. suppression of the hypothalamic–pituitary–adrenal axis or growth).

Topical calcineurin inhibitors are discussed as effective agents, based on studies involving several thousand children. There was consensus that concern remains about potential long-term adverse effects. The paper states that tacrolimus and pimecrolimus should be used as per approved indications. Finally, systemic therapies, including antihistamines, psychosocial interventions, environmental modifications and adjuvant therapies for atopic dermatitis are discussed, with recommendations for further study.

Unfortunately, no algorithm for atopic dermatitis treatment is offered in this statement, nor is the approach to therapy based upon disease severity.

The International Consensus Conference on Atopic Dermatitis II

The International Consensus Conference on Atopic Dermatitis II was held in New Orleans in 2002, and the summary was published in 2003 (2). The management of atopic dermatitis is summarized as comprising disease-adapted treatment with adjuvant basic therapy (skin protection), anti-inflammatory measures as needed, the identification and avoidance of triggers, and focused symptomatic relief with emphasis on skin hydration and reduction of pruritus. A review of standard therapies is similar to those discussed above in the AAD Consensus Conference, with a more detailed discussion of topical pimecrolimus and tacrolimus safety and efficacy.

Treatment strategies and guidelines are given in an algorithm form (Fig. 2). Initial assessment of disease history, extent and severity are considered, including assessment of psychological distress and impact on family. Initial treatment of atopic dermatitis includes emollients for skin hydration and education for both patients and caregivers on the avoidance of trigger

factors. If atopic dermatitis is actively flaring, short-term use of topical corticosteroids is indicated. Topical calcineurin inhibitors are alternatives for acute control of pruritus and inflammation. After disease clearance patients should revert to continuous use of emollients. For maintenance therapy, in cases of disease persistence and/or frequent recurrences, topical calcineurin inhibitors may be used, either at first signs of local recurrence, or as long-term therapy. Intermittent topical corticosteroids are another option for maintenance therapy.

Adjunctive measures are discussed as sometimes necessary to maximize outcomes for individual patients. These include avoidance of trigger factors, management of bacterial or viral infections, psychological interventions, and antihistamines. Severe refractory disease may be managed with phototherapy, potent topical steroids, cyclosporine, methotrexate, oral steroids, azathioprine, and/or psychotherapeutic interventions.

The algorithm presented is succinct, and should be clinically useful. However, it does not define disease severity, nor offer guidelines on when patients should move from one ‘box’ of the algorithm to another.

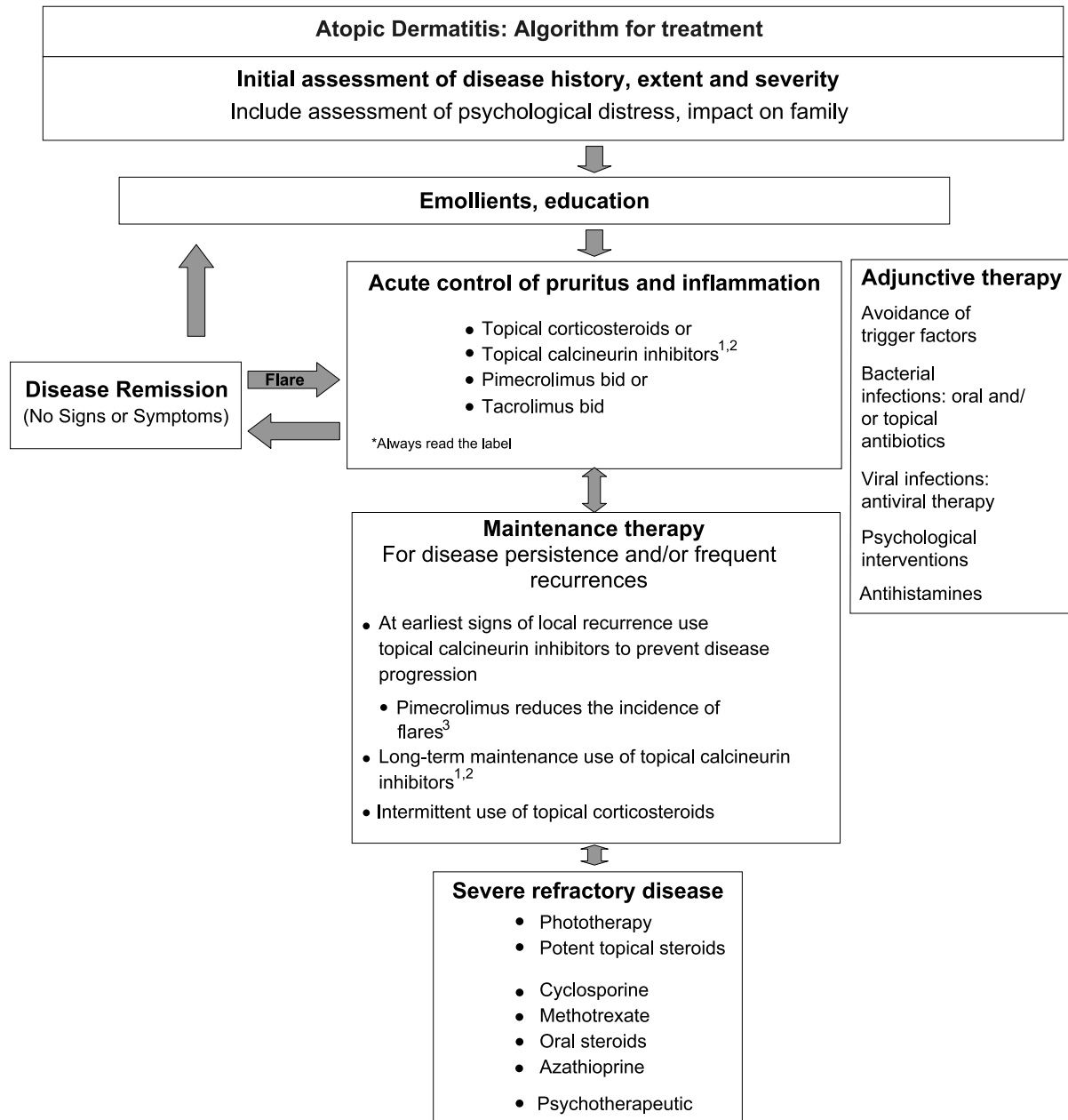
American Academy of Dermatology Guidelines of Care for Atopic Dermatitis

These guidelines were developed through convening a group of experts to determine the audience for the guideline, define the scope and to identify clinical questions to structure the primary issues of diagnosis and management. An evidence-based model methodology [described by Goodman, 1998 (7)] was utilized, with a five-point scale assignment. The guidelines were approved by the AAD in July, 2003 (3).

Unfortunately, these guidelines of care serve more as a composite of evidence with a statement of ‘levels of consensus’ by the experts. Therapies and interventions are evaluated with concise references. No algorithm for care, or specific management guidelines based upon disease severity, are included.

An interesting portion of the guidelines concern preventative measures during pregnancy and after birth. No recommendations are made regarding dietary interventions and aeroallergen avoidance for the mother, as it is stated that there is no conclusive evidence that manipulation prevents atopic dermatitis either in the infant or child. There is also no definitive evidence that exclusive breast feeding, aeroallergen avoidance, and/or early introduction of solid foods influences the development of atopic dermatitis, while there is some evidence that prolonged breast feeding may delay the onset of atopic dermatitis. Probiotic treatment during pregnancy and nursing ‘may delay the onset’ of atopic dermatitis in infants and children.

Recommendations concerning topical corticosteroid use stress that they are the standard of care to which other



1. The evidence of the safety and efficacy of pimecrolimus was derived from studies primarily in patients with mild-to-moderate atopic dermatitis; tacrolimus data was derived from moderate-to-severe patients
2. Pimecrolimus has been studied in clinical trials in infants as young as 3 months, as compared with tacrolimus from 2 years
3. Clinical trial data have proven that pimecrolimus reduces incidence of flares, these trials have not been performed for tacrolimus

Figure 2. ICCAD II algorithm for atopic dermatitis treatment [Reproduced with permission from Blackwell Publishing. Ellis C, Luger T, Abeck D, Allen R, Graham-Brown RA, De Prost Y et al. ICCAD II Faculty. (ICCAD II*): Clinical update and current treatment strategies. Br J Dermatol 2003;148(Suppl. 63):3–10. (2)].

treatments are compared, with summaries of known and possible cutaneous and systemic side-effects. Long-term intermittent application of corticosteroids is judged helpful and safe based on two randomized controlled studies. It is

stated that topical calcineurin inhibitors have been shown to reduce the extent, severity, and symptoms of atopic dermatitis in adults and children. A conservative stance is taken concerning their use, with a statement that

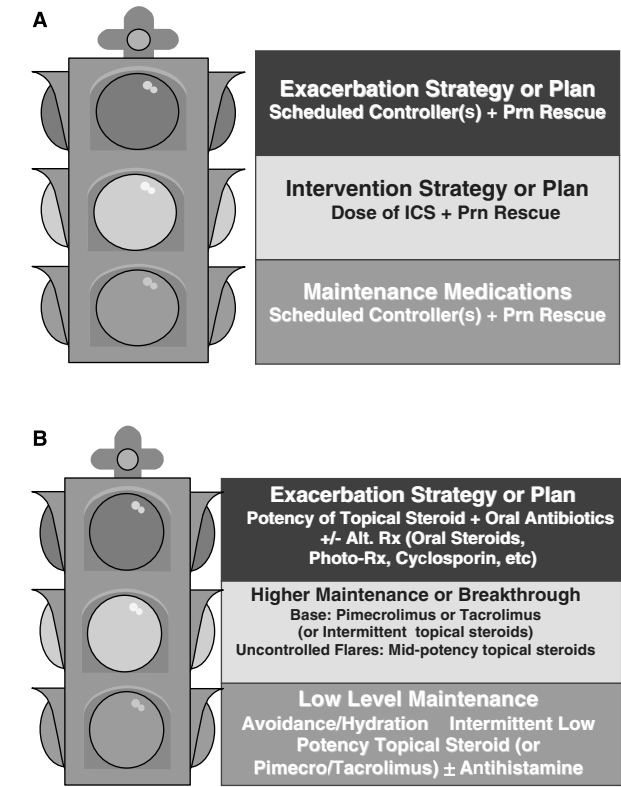


Figure 3. (A) NHBLI traffic light asthma action plan; (B) proposed atopic dermatitis action plan.

‘long-term (greater than 1 year) safety’, including concerns about immunosuppression and malignancy, remains unanswered. The document extensively reviews antibiotic use, systemic agents including antihistamines, evening primrose, fish and borage oil, immunomodulatory agents (cyclosporine, interferon- γ , systemic steroids, and others) and dietary restriction in established atopic dermatitis. Detailed discussion is beyond the scope of this paper.

Parallels with asthma and evolution in guidelines of care

There are clearly parallels between asthma and atopic dermatitis. A seven-member panel representing United States-based specialists in dermatology, allergy, asthma, immunology and pediatrics convened to review the literature and evolving data on atopic dermatitis and asthma, identifying common features of epidemiology, genetic predisposition, immunopathophysiology and evolution of treatment (8). Atopic dermatitis is frequently the first manifestation of an atopic diathesis, which includes asthma and allergic rhinitis. The ‘atopic triad’ has numerous elements of pathophysiology in common, including immunologic and cyclic nucleotide regulatory abnormalities, inflammatory mediators, and allergic triggers.

A. MILD DERMATITIS (Defined by disease extent or persistence)

Step 1	Step 2	Step 3
Emollient bid	Emollient bid	Emollient bid
	Intermittent low potency TS for flare control	Mid-potency TS for flare control
	(? TCI alternative)	TCI alternative
	+/- Antihistamines	+/- Antihistamines

Step forward if necessary, back to step 1 if controlled.
Maintenance Rx beyond step 1 if frequent recurrence or persistence of disease.

B. MODERATE DERMATITIS (Defined by disease extent or persistence)

Step 2	Step 3	Step 4
Emollient bid	Emollient bid	Emollient bid
Intermittent low potency TS for flare control	Mid to higher potency TS for flare control (may be used instead of or in addition to TCI)	Higher potency TS for flare control
TCI alternative	TCI long-term intermittent	TCI long-term intermittent
+/- Antihistamines	+/- Antihistamines	+/- Antihistamines
	Antibiotic if clinical infection	Antibiotic if clinical infection

Step forward if necessary, back one step if controlled.
Maintenance Rx as Step 2 if frequent recurrence or persistence of disease.
Consider Step 5 if uncontrolled: Photo-rx, other systemic rx.

C. SEVERE DERMATITIS (Defined by disease extent or persistence)

Step 3	Step 4	Step 5
Emollient bid	Emollient bid	Emollient bid
		Photo-rx or Systemic Rx
Mid to higher potency TS for flare control (may be used instead of or in addition to TCI)	Higher potency TS for flare control	
TCI long-term intermittent (?Intermittent low to mid-potency TC as alternative)	TCI long-term intermittent	TCI long-term intermittent
+/- Antihistamines	+/- Antihistamines	+/- Antihistamines
	Antibiotic if clinical infection	Antibiotic if clinical infection

Step forward if necessary, back one step if controlled.
Maintenance Rx standard; Step 4 if uncontrolled; Step 5 as needed

Note: Changes in steps are in bold

Figure 4. Proposed algorithm for severity-based step therapy of atopic dermatitis. Note: Good skin care and avoidance of irritants and allergens are part of base therapy preceding step 1.

The panel reviewed the development of guidelines for the diagnosis and management of asthma, by the National Heart, Lung, and Blood Institute (NHLBI) and National Asthma Education and Prevention Program (NAEPP) resulting in *Guidelines for the Diagnosis and Management of Asthma*, published in 1991. This and subsequent reports of the NHLBI (1992), NHLBI/WHO (1995) and a second expert group (1997) have had tremendous impact, heightening awareness of the inflammatory component of asthma, opening new areas of basic science and clinical research, encouraging collaborative work amongst various specialty researchers and physicians, and providing a standardized approach for therapy (9). The seven-member panel concluded that, based upon current information and evolving therapeutic options, a clear rationale exists to support atopic dermatitis guideline development.

Consensus guidelines for therapy in atopic dermatitis: what are we missing?

Ideally, treatment algorithms should be easy to understand, useful, concise but not overly simplistic, and consistent with standards of care for atopic dermatitis. They should also be useful for primary-care physicians, pediatricians, dermatologists, and nonphysician health-care workers, as well as affected individuals and/or their families. Severity-based algorithms may be optimal, though severity evaluation methods are controversial. Of the practice parameters and guidelines discussed above, the ICCAD II algorithm is probably the best, though it does not define disease intervention based upon disease severity.

One successful strategy used for asthma care is a 'traffic light' asthma action plan, defining three levels of intervention. (Fig. 3) The 'green light' section is defined as clinically doing well, 'all clear' with use of medications. Yellow denotes caution, with increase of symptoms requiring increased need for asthma medications. Red signifies medical alert, with persistence of symptoms greater than 24 h, with additional medication needed.

A variation of this traffic light is offered for atopic dermatitis. (Fig. 3B). In this model of care, levels of intervention are based upon disease severity or persistence of disease. The 'green level' represents minimal intervention, with baseline therapy comprised of emollients, good skin care and avoidance of irritants, and intermittent low-strength topical corticosteroids for inflammatory disease, with calcineurin inhibitors as an alternative. The yellow level reflects moderate level disease requiring higher maintenance care and/or

breakthrough flares. Flares may be managed with mid-potency topical corticosteroids, and base maintenance therapy is appropriate with topical calcineurin inhibitors, or intermittent topical steroids as an alternative. The red signifies severe exacerbation, requiring higher potency topical corticosteroids, systemic medication, or phototherapy.

An alternative algorithm is offered based on disease severity (Fig. 4). Severity assessment for entry into the algorithm may be based on extent of disease and/or persistence of disease. It assigns 'steps of therapy', similar to NHLBI and NAEPP asthma guidelines. Different severity of atopic dermatitis prescribes a different 'base step' of therapy. This algorithm has not been evaluated in clinical practice.

Any algorithm utilizing disease severity will require clinically simple and useful category assignments. Commonly used severity ratings scales are numerous, competitive and vary in how 'objective' they are (10–12). They pose difficulties in their utilization for clinical purposes, most utilizing scoring systems that attempt to objectively assign numbers for components that get assessed subjectively. The most commonly used and validated scales, such as the SCORAD and EASI, as well as recently proposed scales based on transepidermal water loss and skin hydration (the Objective Severity Assessment of Atopic Dermatitis, or OSAAD), are very difficult to use in clinical practice (5,6,13,14). Also, most severity scales do not generally assess disease activity over time, and cannot distinguish the patient with very intermittent flares of atopic dermatitis involving a moderate amount of body surface area, easily controlled with several days of topical steroids and continued emollients, with one with persistent dermatitis over the same body surface area, or one with rapid recurrence with discontinuation of steroids. One method is to assign severity (e.g. mild, moderate, or severe) by the medications needed to keep the disease under control. Another more practical method may be simple assignment into these categories based upon disease extent and persistence.

Conclusion

It is hoped that the evolution of understanding of the pathogenesis of atopic dermatitis and of therapeutic alternatives will allow the development of consensus on diagnosis and treatment. Treatment algorithms may be useful in improving atopic dermatitis control over a long-term basis, perhaps influencing the overall course of the disease, or the progression of atopy.

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